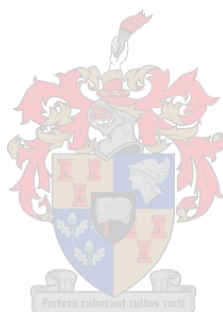


Applications of Inherently Chiral Calix[4]arenes

by

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*Thesis presented in partial fulfilment of the requirements for the degree
Master of Science in Chemistry at the University of Stellenbosch.*

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March 2013

Declaration

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Abstract

Calixarenes are large cyclic molecules that have a distinctive bowl-shaped geometry. The nonplanar nature of these molecules means that, by selectively functionalizing the calixarene on one side of the symmetry plane, one introduces inherent chirality. As with other varieties of chirality, this asymmetry can be utilised to impart stereoselectivity to the formation of new bonds through asymmetric catalysis. The evaluation of inherently chiral calixarenes has been hindered thus far by the difficulty in obtaining enantiomerically pure samples. Using a recently developed stereoselective methodology, incorporating chiral oxazoline directed ortholithiation, the synthesis of a series of upper-rim *meta*-substituted inherently chiral calixarenes is described. With the use of this methodology, the desired calixarene ligands are synthesised in high diastereoselectivity (from 75% de to >99% de).

The inherently chiral *meta*-substituted bidentate thioether-oxazoline calixarenes synthesised were subsequently investigated as asymmetric ligands for palladium catalysed allylic alkylation. The debutylated series of calixarenes showed good catalytic efficiency, achieving high levels of conversion (>90% isolated yield). A rate enhancement relative to a planar model system was observed. Moderate levels of enantioselectivity (31% ee to 89% ee) were achieved. The influence of the central chirality of the chiral oxazoline was determined to be the predominant stereoselective effect. Increasing the steric bulk on this chiral carbon resulted in a significant increase in the stereoselectivity. Inherent chirality was found to have a subtle but significant effect.

Increasing the steric bulk on the calixarene bowl, through the use of analogous *tert*-butylated calixarene, had an adverse effect on the catalytic efficiency. These ligands formed unstable complexes that decomposed before any appreciable yield of the desired product could be formed.

Opsomming

Calixarene is groot sikliese molekule met 'n kenmerkende bak-vormige meetkunde. Die nie-planêre aard van hierdie molekules beteken dat selektiewe funksionalisering van die calixareen op een kant van die simmetrievlak vorm 'n inherente chirale molekule. Soos met ander soorte van chiraliteit, hierdie asymmetrie kan gebruik word om stereoselektiwiteit aan die vorming van nuwe bindings aan te dra, deur middel van asimmetriese katalise. Die evaluering van inherente chirale calixarene dusver is verhinder deur probleme in die verkryging van enantiomeerisuiwer monsters. Met behulp van 'n onlangse ontwikkelde stereoselektief metodologie, waarin 'n chirale oksasolien gerig ortolitiëring, die sintese van 'n reeks van boonste rand *meta*-gefunktionaliseerde inherent chirale calixarene word beskryf. Met die gebruik van hierdie metodologie, word die verlangde calixareen ligande gesintetiseer in hoë diastereoselektiwiteit (van 75% tot 99% do).

Die inherente chirale *meta*-gefunktionaliseerde tio-eter oksasolien calixarene gesintetiseer is daarna as asimmetriese ligande vir palladium-gekataliseerde allyliese alkilering ondersoek. Die gedebuteleerde reeks van calixarene het goeie katalitiese effektiwiteit getoon, met die bereiking van hoë vlakke van omsetting (> 90% geïsoleerde opbrengs). 'n Tempoverbetering relatief tot 'n planêre modelstelsel is waargeneem. Gematige vlakke van enantioselektiwiteit (31% ee tot 89% ee) is behaal. Die invloed van die sentrale chiraliteit van die chirale oksasolien is bepaal as die oorheersende stereoselektiewe effek. Die verhoging van die steriese massa op hierdie chirale koolstof het gelei tot 'n beduidende toename in die stereoselektiwiteit. Inherente chiraliteit is gevind om 'n subtiele, maar betekenisvolle uitwerking te hê.

Die verhoging van die steriese grootmaat op die calixarene bak, deur die gebruik van analoog *tert*-butieleerde calixarene, het 'n nadelige uitwerking op die katalitiese effektiwiteit. Hierdie ligande vorm onstabiel komplekse dat ontbind voordat enige aansienlike opbrengs van die verlangde produk kan gevorm word.

Acknowledgements

I want to express my heartfelt gratitude to my supervisor, Dr Gareth Arnott, for his enthusiasm for and extensive knowledge of organic chemistry, as well as his patience, guidance and leadership.

My thanks go out to all the members of the Group of Medicinal and Organic Chemistry, past and present, who were always there when there was a problem in the lab or the office. A special thank you to Simon Herbert, for his outstanding knowledge and experience. Additional thanks to my labmates Dewald Kleinhans, Malcolm Applewhite, Leon Jacobs, Luke Hodson, Anton Hamann and Lonwabo Ngodwana, for always being there for help when I needed it (even if only to get chemicals off the high shelves!), and for creating a working environment that was never short of amusement!

To all my friends in the Department of Chemistry, especially Helene Wahl and Leigh Loots. I don't think I would have made it through some days if not for lunchtime gatherings in the De Beers quad, where we could all laugh and talk, and where many problems were discussed and solved. A special thanks to my friends outside of chemistry, especially my brother, Michael. Thank you for not only putting up with me when I went off on long chemical discussions that no-one understood, but actually listening. I also want to extend my eternal gratitude to all my friends and family who read through my work and offered their advice.

My utmost thanks to my parents, Peter and Marian. All my life, you have encouraged me to do my best, and have given me every opportunity to follow my dreams. Words cannot express how grateful I am for your unending love and support.

Additional Acknowledgements

Stellenbosch University, for providing me with the wonderful opportunity to study at this amazing institution.

The staff (academic and technical) within the Department of Chemistry and Polymer Science, especially those in the De Beers Building, without whom this research could never have been accomplished.

The National Research Foundation for funding.

The Central Analytical Facility for assistance with the analytical work for my studies.

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List of Technical Abbreviations

ATR-IR	Attenuated Total Reflection Infrared Spectroscopy
c-PentLi	Cyclopentyl lithium
de	Diastereomeric Excess
dr	Diastereomeric Ratio
ee	Enantiomeric Excess
ESI	Electrospray Ionization
IR	Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
TLC	Thin Layer Chromatography

Chapter 1

General Introduction

1.1. Review of Calix[4]arene Chemistry

1.1.1. Introduction to calixarenes

For the last 30 years, there has been a focused interest on the unique chemical properties of calixarenes. Many of these properties are a result of their bowl- or cup-shaped nature, which gives distinct differences between the inner and outer faces (Figure 1.1).¹ Calixarenes have been used in a wide variety of fields, including (but not limited to) employing them as ligands for metal catalysed asymmetric reactions,² the storage and separation of gaseous compounds,^{3,4} as ligands in asymmetric catalysis⁵⁻⁸ and as enzymatic mimics or molecular receptors.⁹⁻¹² The nonplanar nature of calixarenes makes it possible to functionalise them to create inherently chiral molecules.

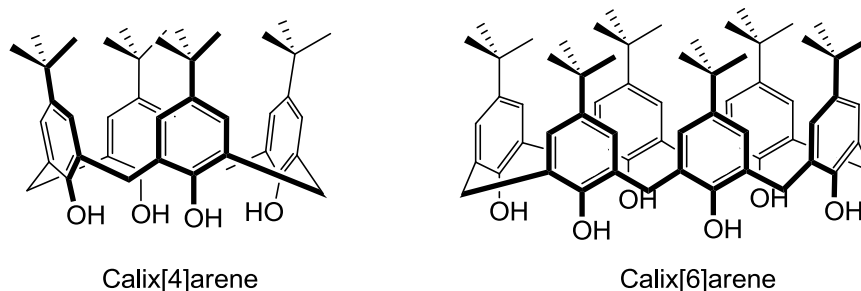


Figure 1.1: Two examples of *p*-tert-butyl-calix[n]arene

1.1.2. The early beginnings

Calixarene chemistry has a rather fascinating background, with its origins in the 19th century. The field of phenol-formaldehyde chemistry was first reported by Adolph von Baeyer. Baeyer is best known for his work on the synthesis and structure elucidation of indigo, and was the recipient of the Nobel Prize in Chemistry in 1905 “in recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds”.¹³ In 1872, Baeyer began work investigating the reaction of phenols with formaldehyde, with the use of acid catalysis. He published three papers that year on his

results. The first paper¹⁴ describes his initial observations, where mixtures of aldehydes and phenols thickened to the point of forming a “kittartige substanz” (cement-like substance). His second paper¹⁵ deals with specific examples (as he tried to control the reactions), such as the reaction of benzaldehyde with pyrogallol, which yielded a red-brown resin. It was only in his third paper¹⁶ that Baeyer introduces formaldehyde as a reactant. Investigations with formaldehyde were limited at the time, as it was a very rare chemical and had to be prepared by Baeyer himself.¹ Baeyer showed that formaldehyde would react with phenols in a similar manner to the larger aldehydes, again giving resin-like products. Unfortunately, he was not able to isolate any pure material from these reactions, and consequently could not perform elemental analyses or propose possible structures for these products. Even though Baeyer did not succeed in characterising his products, he provided a valuable start to phenol-formaldehyde chemistry.

1.1.3. Moving towards control

Towards the end of the 19th century, two independent German chemists were studying the condensation of phenol and formaldehyde, this time under basic conditions.^{17, 18} This reaction yielded both *ortho*- and *para*-methylhydroxy phenol, rather than resinous tars (Figure 1.2). Their success resulted from the use of much milder and better controlled conditions, as opposed to Baeyer’s very strenuous conditions.

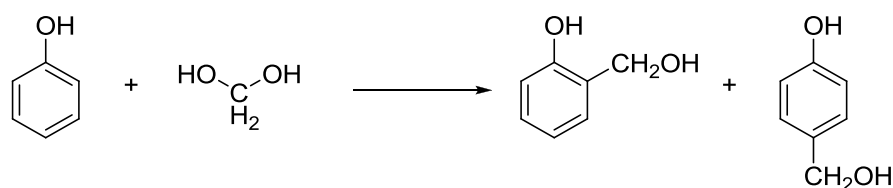


Figure 1.2: Products obtained by controlled base-induced reaction of formaldehyde and phenol

At the turn of the 20th century, more than 25 years after Baeyer’s work, the field of phenol-formaldehyde chemistry was still largely uncharted. A number of chemists had tried to gain better control over the reaction, or to find a practical application for the resin-like products, but had failed.¹⁹⁻²² The first true victory went to Leo Baekeland. His research showed that using a

very small, controlled amount of base was vital for obtaining a usable resin.¹ His work was first patented in 1907, as Bakelite:²³ the first entirely synthetic plastic. This field was ultimately a huge commercial success for Baekeland, yielding over 400 patents.¹

A breakthrough for calixarene chemistry came in the early 1940s when Zinke and Ziegler realised that the reaction could be simplified through the use of *para*-substituted phenols.^{24, 25} Phenol itself is activated in the *ortho* and *para* positions, which yields complex, crosslinked polymers – hence the resinous products. By blocking off the *para* position, only linear oligomers can be obtained. Their reaction of formaldehyde with *p*-tert-butylphenol yielded a crystalline product, which melted/decomposed at temperatures exceeding 300 °C. They obtained products of this type using a variety of R-groups. After further study, they proposed a cyclic tetrameric structure (Figure 1.3).

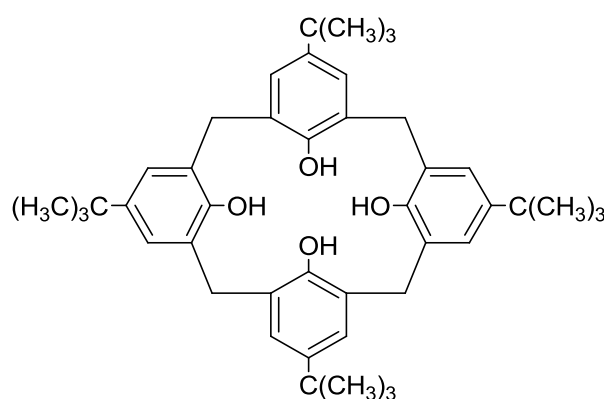


Figure 1.3: Cyclic tetrameric structure of base-induced product

This ideal of a cyclic structure was under discussion by academics at the time. Niederl and Vogel had been investigating the acid-catalysed condensation of aldehydes and resorcinol, and had suggested the structure of these compounds to be a cyclic tetramer.²⁶ The cyclic products were later proved by Hayes and Hunter, who synthesised the same phenol-formaldehyde products via a stepwise synthesis.²⁷

The process through which the various calixarenes can be formed is highly complex, and there is still disagreement regarding the mechanism of cyclisation.¹ The formation of the linear oligomers, however, can be put forward mechanistically through the condensation of formaldehyde and phenol (Figure 1.4). This condensation forms hydroxymethyl phenol units,

Chemical reaction scheme showing the base-catalyzed polymerization of 4-substituted phenols to form linear oligomers. The scheme starts with a 4-substituted phenol (R-phenol) reacting with hydroxide (HO^-) to form a phenoxide ion. This ion undergoes nucleophilic attack on formaldehyde (HCHO) to form a hydroxymethyl-substituted phenoxide intermediate. Subsequent proton transfer and further reaction with another formaldehyde molecule leads to a dihydroxymethyl-substituted phenoxide. This intermediate then reacts with a second 4-substituted phenol molecule, displacing the phenoxide group to form a dimer. The process repeats, leading to the formation of linear oligomers.

The length of the linear oligomers, and consequently the cyclic calixarenes, can span a wide range. Long polymeric chains are known, as well as calix[n]arenes with n values between 4 and 20.²⁸ Extensive methodological research has been done to allow the chemist to selectively synthesise the desired calix[n]arene by carefully selecting and controlling the reaction conditions. These conditions include the reaction temperature and the nature and concentration of the base used.¹

1.1.4. Calix[4]arene Regions and Conformations

1-4

transformation, i.e. lower rim (exo) functionalised calixarenes,^{31, 32} upper rim (endo) functionalised calixarenes^{33, 34} and bridge functionalised calixarenes.³⁵

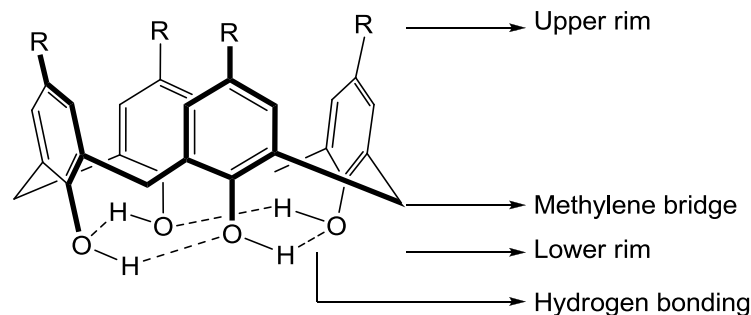


Figure 1.5: The regions of a calix[4]arene in the cone conformation

Calix[4]arenes display a remarkable degree of flexibility, allowing them to exist in a variety of conformations.³⁶ Calix[4]arene adopts the cone conformation in the solid state, driven by the octameric hydrogen bonding that exists between the phenolic residues.¹ The hydrogen bonding is cooperative, exists in either a clockwise or anticlockwise directionality and greatly increases the stability of the calixarene.³⁷ In solution, it has been found that calix[4]arenes can undergo inversion through the annulus. This inversion occurs rapidly, even at room temperature, and can be seen as analogous to the inversion of cyclohexane systems.^{30, 38}

As the calixarene inverts (Figure 1.6), the groups present on the bridging carbon convert between an axial and an equatorial position.^{1, 38, 39}

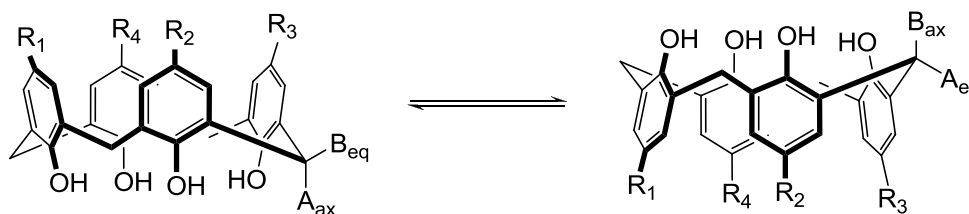


Figure 1.6: Inversion of calix[4]arene in solution

Solution-state inversion can be prevented by lower rim functionalisation to increase the steric bulk of the phenolic positions. This is typically achieved through etherification or esterification.^{1, 28} With the destruction of the hydrogen bonding fixing the calixarene in the cone conformation, several different conformations may be observed. These include the partial cone, the 1,2-alternate and the 1,3-alternate (Figure 1.7).

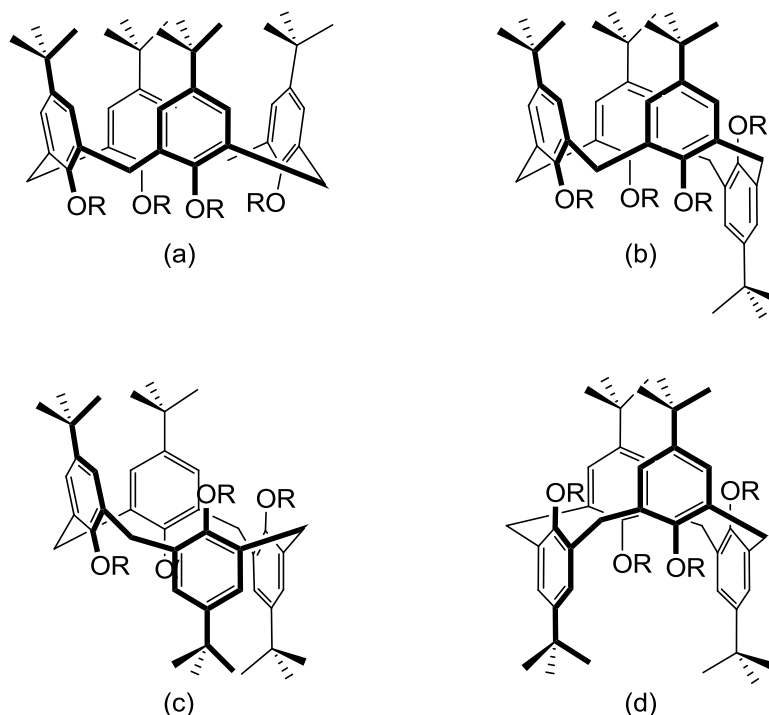


Figure 1.7: Conformations of *p*-*tert*-butyl calix[4]arene. (a) Cone, (b) Partial cone, (c) 1,2-Alternate and (d) 1,3-Alternate

1.1.5. Calix[4]arenes and Symmetry

The parent calix[4]arene compound in the cone conformation has C_4 symmetry. Lower rim functionalisation distorts the symmetry of the cyclic compound to a C_{2v} conformation known as the pinch cone, where two opposite rings are positioned upright, while the remaining two rings are further apart and angle outward (Figure 1.8). The loss in symmetry can be seen in the ^1H NMR by examining the signals representing the axial and equatorial hydrogens on the methylene bridges.

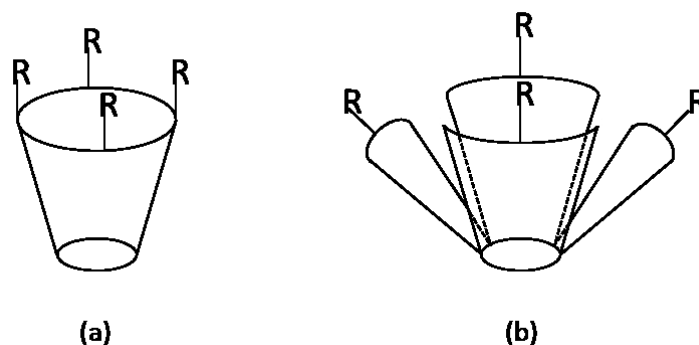


Figure 1.8: The cone and pinched cone conformations

Upper rim functionalisation can lead to a variety of products, namely mono-functionalised, distal-functionalised (two opposite rings), proximal-functionalised (two adjacent rings), tri-functionalised or tetra-functionalised. The functionalisation pattern of the upper rim can be described by a nomenclature first described by Shinkai and coworkers.^{40, 41} For example, the parent (un-functionalised) calixarene in the cone conformation would be described as AAAA with C_4 symmetry (Figure 1.9).

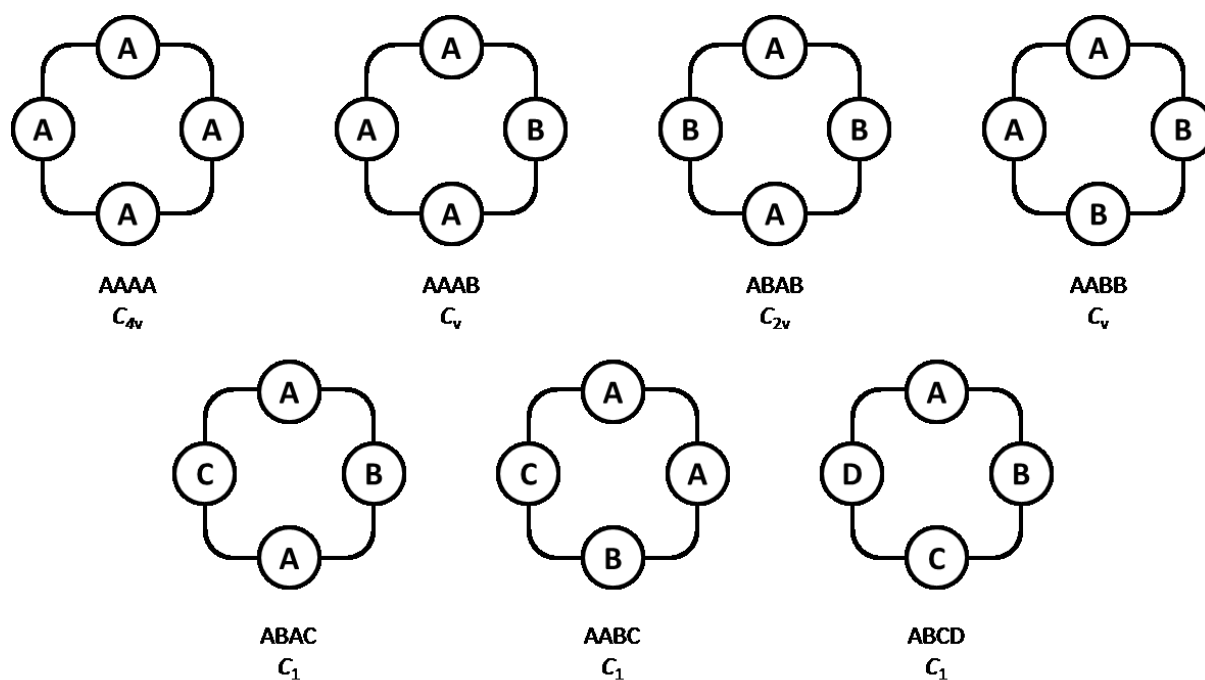


Figure 1.9: Systematic classification of functionalised calixarenes

The three dimensional and asymmetric nature of the C_1 calix[4]arenes creates the potential for inherently chiral calix[4]arenes.^{40, 41} On inspection, one can see that for the AABC and ABCD configurations, the mirror image of the calixarene would be non-superposable and therefore these molecules are chiral. The property of inherent chirality is decidedly interesting and has sparked a field of further study.

1.1.6. Inherent chirality in calix[4]arenes

Chirality arises from asymmetric functionalisation, and is not limited to conventional sp^3 chirality. Chirality can also be a consequence of the overall three-dimensional nature of a compound, such as in the case of calix[4]arenes.⁴² Two common examples of this are axial chirality (such as that present in BINAP compounds)^{43, 43} and planar chirality (such as that present in ferrocenyl compounds)^{44, 45} (Figure 1.10). Other forms of non- sp^3 chirality include helical chirality present in DNA,⁴⁶ as well as helicenes,⁴⁷ and inherent chirality as seen in calix[4]arenes.¹

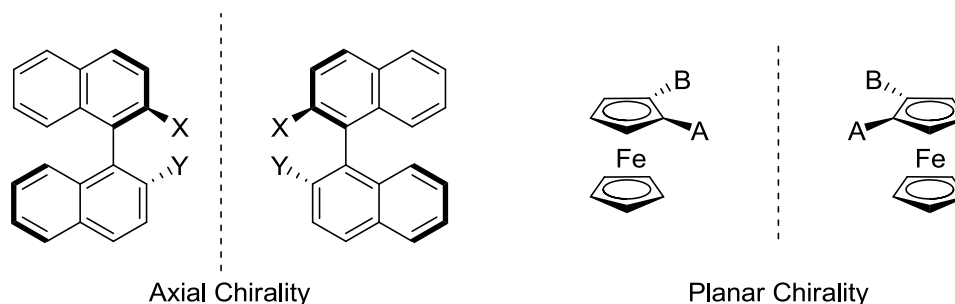


Figure 1.10: Two forms of non- sp^3 chirality

Inherent chirality arises from the functionalisation of a non-planar molecule on one side of the symmetry plane. Szumna specifies the definition “*inherent chirality arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation*”.⁴⁸ The bowl- or cup-shaped nature of calixarenes makes this type of functionalisation possible.¹ This was first demonstrated by Gutsche in the early 1980s.⁴⁹

Functionalisation to yield an inherently chiral calixarene can take place at the upper rim, lower rim or methylene bridges. An example would be the previously mentioned AABC and ABCD upper rim functionalisation patterns. The scope for creating inherently chiral calix[4]arenes is consequently rather vast. In addition to this, upper rim functionalisation can also be concentrated on a single ring, by introducing different groups into the *para* and *meta* positions (relative to the phenolic position), as shown in Figure 1.11. When using Shinkai's nomenclature, these *meta*-functionalised rings are indicted with an asterisk (*).

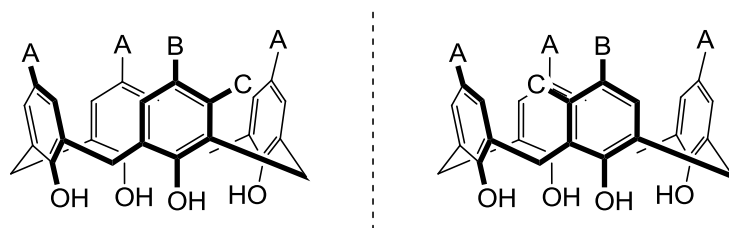


Figure 1.11: A *meta*-functionalised calixarene, denoted AAAB*

As previously discussed, calix[4]arenes are able to rapidly invert in solution (see Figure 1.6). Just as the methylene axial and equatorial protons interconvert, so too will the chirality introduced by upper rim modification. This introduces a problem, as an inherently chiral calixarene will be in equilibrium with its enantiomer in solution (Figure 1.12). If one wishes to fix the calixarene in one form, it is essential to functionalise it such that inversion is impossible (as discussed in Section 1.1.4).

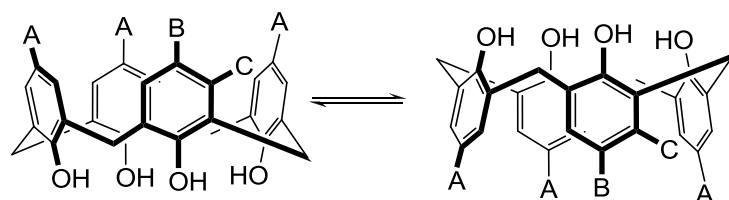


Figure 1.12: Interconversion of inherently chiral calixarene in solution

Until recently, the difficulty in obtaining enantiomerically pure samples has severely hampered the evaluation of inherent chirality in calix[4]arenes.^{50, 51} Initial attempts to synthesise these compounds were laborious, requiring either step-wise synthesis of the linear oligomers before cyclisation to form the calixarene, or resolution methods to separate the enantiomers.^{40, 42, 49}

Advancements in calixarene chemistry in the 1990s finally allowed the synthetic chemist to desymmetrise the calixarene without the need for a step-wise synthesis of the bowl. Most selective functionalisation pathways utilize partial functionalisation of the lower rim, and methods exist for controlled mono, di (proximal or distal) or tri-functionalisation.¹ The most commonly used method is selective esterification⁵² or etherification^{32, 34} of the lower rim. This modification alters the electronic properties of the rings, which results in the potential for selective functionalisation of the upper rim³⁴ through halogenation,^{53, 53} nitration³³ and aryl- or alkylation.^{1, 54} The *t*-butyl groups of the calixarene can also be removed through reverse Friedel-Crafts alkylation.^{31, 55}

Recently, our group developed the first stereoselective method for the synthesis of upper-rim *meta*-substituted inherently chiral calix[4]arenes (Figure 1.13).⁵⁶ This was accomplished through the use of a chiral oxazoline-directed *ortho*-lithiation and resulted in high selectivities (93% de). Through further refinement of the reaction conditions and the oxazoline directing group, the selectivity has been further increased (98% de).⁵⁷ With the development of a reliable method for obtaining a variety of *meta*-substituted calix[4]arenes, our group was in a position to evaluate whether the inherent chirality of these molecules would have any effect imparting asymmetry into prochiral metal-catalysed reactions.

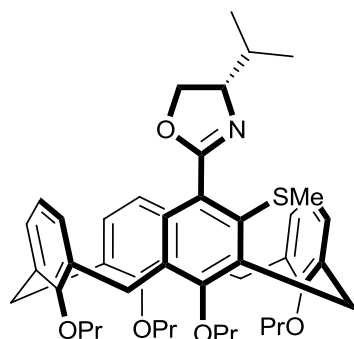


Figure 1.13: An example of the inherently chiral calix[4]arenes in this study

1.2. *Asymmetric catalysis*

1.2.1. *Metal-catalysed reactions*

Transition metals are used in organic chemistry as catalysts for a variety of synthetically useful pathways and are particularly useful because they offer high levels of chemo-, regio- and stereoselectivity.⁵⁸⁻⁶¹ Reactions catalysed by palladium have become a valuable tool for organic chemists^{62, 63} and cover a range of transformations, including Heck reactions,⁶³ Stille couplings,⁶⁴ Wacker oxidations⁶⁵ and allylic substitutions.^{66, 67} An important characteristic of the catalysts for all these reactions is the ability of the metal centre to undergo oxidative addition and reductive elimination – something palladium is able to do with ease.⁶⁷

1.2.2. *Oxazoline-containing ligands in asymmetric catalysis*

Oxazoline-containing compounds have been found to be some of the most successful and versatile ligands for asymmetric catalysis as a result of their facile synthesis, as well as the fact that they are easily modified.⁶⁸ Almost all oxazoline ligands are synthesised using chiral amino alcohols (in turn derived from the reduction of amino acids). Consequently, the chiral centre on the oxazoline is adjacent to the coordinating nitrogen atom; close enough to the metal centre to have a significant influence on its geometry.

A vast array of mono(oxazoline), bis(oxazoline), tris(oxazoline) and tetra(oxazoline) ligands have been reported in the literature, with coordination occurring between the oxazoline nitrogen and a neighbouring phosphorus, nitrogen, oxygen or sulfur atom.⁶⁸ For the purposes of this study, only mono-oxazoline *N,S*-ligands will be discussed.

Claver synthesised a series of simple oxazoline thioether ligands (Figure 1.14) and tested them as ligands for the iridium-catalysed hydrogenation of *N*-(α -methyl)benzylidenebenzylamine.⁶⁹ The results reveal moderate to complete conversion (30-100%). However, only one ligand ($R = \text{Me}$, $R' = \text{Ph}$) displayed any enantioselectivity, at 15% ee.

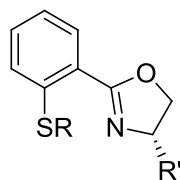


Figure 1.14: Oxazoline thioether ligands tested by Claver⁶⁹

R = Me, Ph or *t*-Bu; R' = Ph, or *i*-Pr

Ricci and coworkers reported the synthesis of thiophene oxazoline ligands (Figure 1.15 (a)), which were used as ligands for palladium-catalysed allylic substitution.⁷⁰ These ligands gave high yields of the desired product (>90%) with good enantioselectivity (70-74% ee). Interestingly, both the (*R*)- and (*S*)-enantiomers of the ligand produced the (*S*)-configured product. Ricci also synthesised a series of ligands with a more rigid, fused tricyclic framework (Figure 1.15 (b)), which were successfully employed as ligands for copper-catalysed conjugate addition of diethylzinc to chalcone, with moderate yields and enantioselectivities.⁷¹ An addition to this work involved oxazoline dithianes. These compounds gave excellent yields (>94%) and good enantioselectivity (up to 90%) for palladium-catalysed allylic alkylation.⁷²

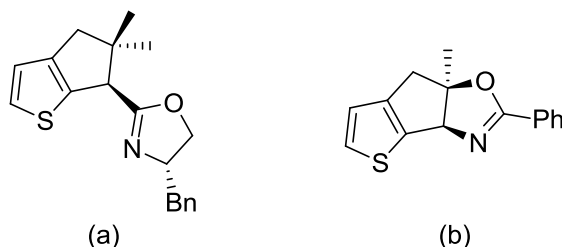


Figure 1.15: Examples of the oxazoline ligands presented by Ricci^{70, 71}

(compounds shown displayed the highest enantioselectivity in their respective studies)

Chiral ligands are not limited to sp^3 point chirality. The concept of planar chirality has been successfully employed in several commercial ligands for metal-catalysed transformations. Much research has been performed on the effect that planar chirality in ferrocenyl-oxazoline derivatives have as ligands for these reactions. Dai and coworkers⁷³ synthesised several oxazolinylferrocene compounds with planar chirality (Figure 1.16), using Ahn's diastereoselective synthesis.⁷⁴ They showed that high enantioselectivity could be achieved

through the use of these thioether-oxazoline as ligands in palladium-catalysed allylic substitution.^{73, 75} However, there was only a moderate difference in the enantiomeric excesses obtained by the two diastereomers of a compound, with both yielding the (*S*) product when applied to the palladium-catalysed reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. They then synthesised an analogue with an achiral oxazoline ring: when tested under the same conditions, this produced only 8.5% ee. They concluded that this small effect from the planar chirality had a match/mismatch effect with the central chirality of the oxazoline ring, which was primarily responsible for the chiral induction observed. The work was later followed up with a more extensive library of planar chiral ferrocenes, which obtained high enantioselectivity when used as ligands for palladium-catalysed allylic substitution and amination reactions.⁷⁵

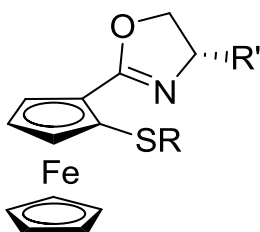


Figure 1.16: The general structure of the ligands investigated by Dai⁷³

R = *i*-Pr, Bn or *t*-Bu; R' = Me, Ph or Tol

1.2.3. *Inherently chiral calix[4]arenes in asymmetric catalysis*

Although inherently chiral calixarenes have been considered as ligands for asymmetric catalysis since their infancy, there are few reports in the literature presenting this application. The difficulty in obtaining enantiomerically pure samples has been hindered by the need for complex synthesis and optical resolution.

In 2001, Matt and co-workers⁷⁶ reported the synthesis of inherently chiral (AABC) diphosphine calix[4]arenes (Figure 1.17). They tested their compounds for catalytic activity in palladium-catalysed allylic alkylation, as well as hydrogenation. The complexes that were tested displayed good activity and moderate enantioselectivity. They concluded that a larger size difference between auxiliary groups led to increased enantioselectivity. Additionally, having the two phosphine groups proximal to each other was significantly more effective than having them situated distally. The presence of additional chiral groups did not add any appreciable chiral induction.

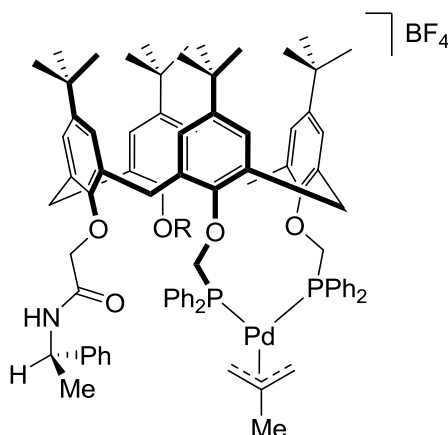


Figure 1.17: Palladium-calixarene complexes evaluated by Matt *et al.* for allylic alkylation
(R = H, SiMe₃ or CH₂C(O)NHC*(Me)Ph)⁷⁶

In 2008, Chen and Huang synthesised a diastereomeric pair of meta-substituted inherently chiral calix[4]arenes possessing an L-prolinamido auxiliary (Figure 1.18).⁷⁷ They found that these calixarenes could be successfully employed as organocatalysts for aldol reactions between ketones and aromatic aldehydes, with enantiomeric excesses up to 94%. Huang and Chen also synthesised a series of novel *N,O*-chiral ligands derived from enantiopure inherently chiral calixarenes, in both cone and partial cone conformations.⁷⁸ These ligands were applied to an asymmetric addition of diethylzinc to benzaldehyde, with high activity but low enantioselectivity.

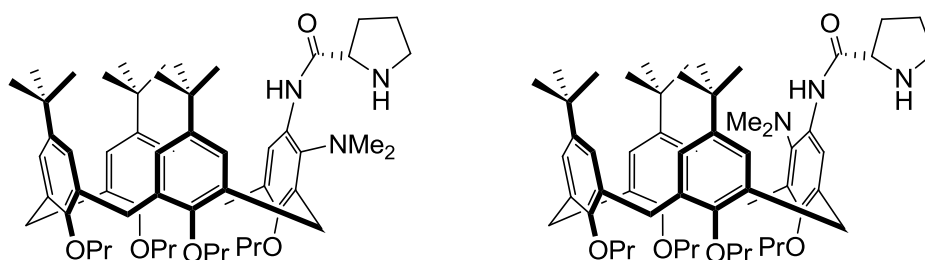


Figure 1.18: The diastereomeric pair of calixarenes synthesised by Huang and Chen⁷⁷

In the same year, Shimizu⁷⁹ reported the synthesis and resolution of an enantiomeric pair of inherently chiral calix[4]arenes (Figure 1.19), as well as an additional series of analogues. A preliminary catalytic investigation set both enantiomers as organocatalysts for an asymmetric Michael addition of thiophenol to cyclohexanone. Both calixarenes displayed good activity, giving excellent yields; however, enantioselectivity was low (15% ee). Despite the poor

selectivity, chiral induction was observed – an important result, as this represented the first reported catalytic activity of an inherently chiral calixarene without a chiral residue.

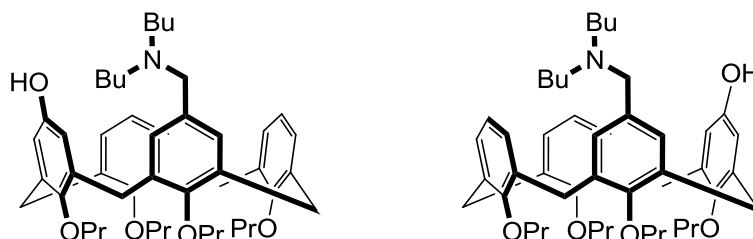


Figure 1.19: An enantiomeric pair of calixarenes synthesised by Shimizu and co-workers⁷⁹

In 2009, Shimizu and Shirakawa⁶ expanded on their work by synthesising an enantiomeric pair of calixarenes derived from a novel inherently chiral calix[4]arene amino acid (Figure 1.20). These compounds were also investigated as organocatalysts for the asymmetric Michael addition reaction. Both enantiomers gave the desired product in 71-73% yield. Chiral induction was 15% ee for both enantiomers, comparable with their earlier published results. The quaternary ammonium salts of these calixarenes were also synthesised and tested as chiral phase-transfer catalysts, where they gave excellent yields (>97%) but poor enantioselectivities (3-6% ee).

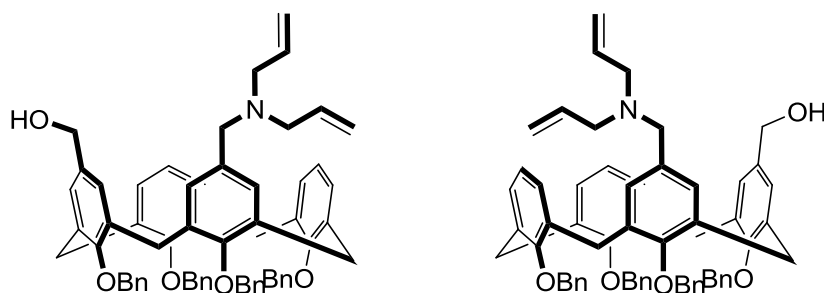


Figure 1.20: Shimizu's inherently chiral calixarenes⁶

1.3. Project aims

We set out to investigate what effect the inherent chirality present in *meta*-substituted bidentate oxazoline calix[4]arene ligands would have in metal-catalysed organic transformations.

There are currently few reports in the literature of inherently chiral calix[4]arenes being used for asymmetric catalysis. Those examples which are presented, typically involve a racemic synthesis, followed by an enantiomeric resolution – rather than a selective synthesis to yield an optically active product.

This project involved the diastereoselective synthesis of a series of inherently chiral calix[4]arenes, as well as a series of planar model compounds. These molecules would all then be applied as ligands in a typical palladium-catalysed reaction to investigate their efficacy. Based on a literature review of chiral ligands possessing similar motifs, it was decided to apply our calix[4]arenes as ligands for the palladium-catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.

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Chapter 2

Synthesis of Ligands

2.1. Retrosynthetic Analysis

The targeted ligands were mono-oxazoline thioether calix[4]arenes. The synthesis of these calix[4]arenes had previously been achieved in our group.^{1, 2} A retrosynthetic analysis of the target calix[4]arene ligands can be seen in Figure 2.1. The thioether functionality could be introduced *via* ortholithiation, using a chiral oxazoline as the directing group. The oxazoline could in turn be disconnected by means of a functional group interconversion (FGI) to the carboxylic acid. The carboxylic acid could be produced through the carboxylation of a mono-halogenated intermediate. The mono-bromo calix[4]arene could be synthesised using established literature procedures from the parent *tert*-butyl calixarene.

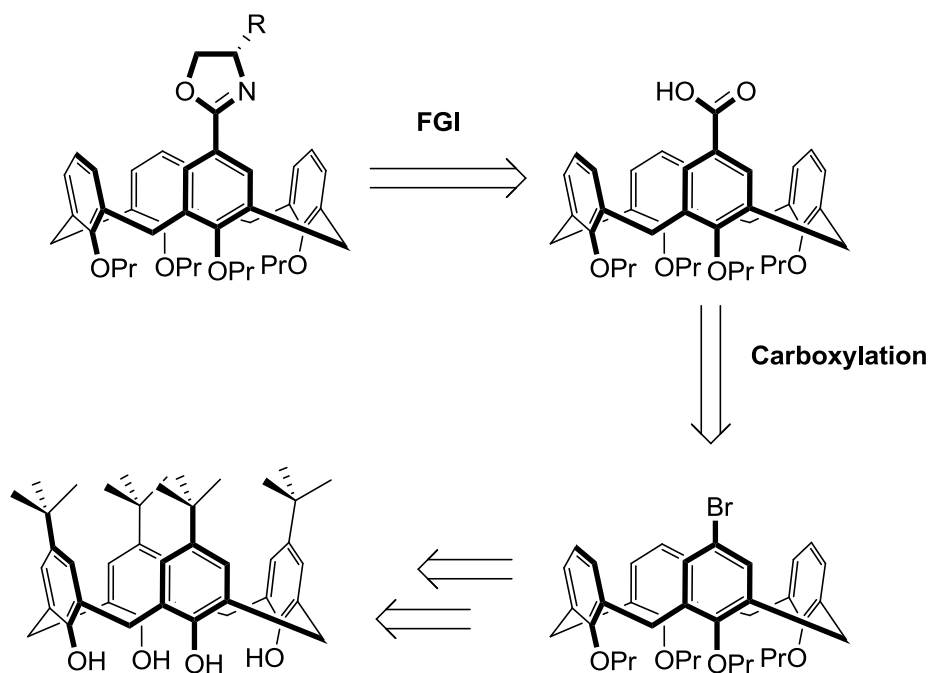


Figure 2.1: Retrosynthetic analysis of target molecule

Three different series of ligands were envisioned. The desired thioether oxazolines could be synthesised both with and without *tert*-butyl groups on the calix[4]arene framework, in order to evaluate the effect differing steric bulk on the calixarene bowl would have when these compounds

are employed as chiral ligands. Within each series, both the isopropyl and *tert*-butyl oxazolines would be synthesised, to evaluate the effect steric bulk on the chiral centre will have in asymmetric catalysis. In addition to the calix[4]arene ligands, a series of planar model compounds would also be synthesised.

2.2. Synthesis of Parent *t*-Butyl Calix[4]arene

One of the most established procedures for the synthesis of calix[4]arenes is through the use of *p*-*tert*-butylphenol in a method first described by Zinke.³ This procedure was modified by Cornforth⁴ and Gutsche^{5,6} and further optimised by Biali.⁷ Formaldehyde and sodium hydroxide were added to *p*-*tert*-butylphenol and the mixture was heated rapidly to 120 °C with mechanical stirring. After approximately 30 minutes, the mixture had turned into a solid yellow-green foam. The flask was immediately removed from the heat source. Diphenyl ether was added and the mixture stirred until the foam was sufficiently agitated to form an easily stirred heterogeneous mixture. Toluene was added to assist the removal of water: by heating to 180 °C, water and toluene were driven off as an azeotrope. This was followed by heating in refluxing diphenyl ether for 4 hours. Once the reaction had been cooled down to room temperature, ethyl acetate was added to the brown solution and the contents of the flask stirred for an additional hour. The filtered product was triturated with acetic acid, producing the desired *p*-*tert*-butylcalix[4]arene **1** in 74% yield without the need for additional purification (Figure 2.2).

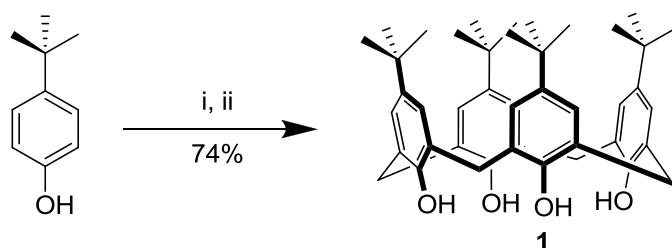


Figure 2.2: Synthesis of parent calix[4]arene **1**. i) CH₂O (1.25 eq), NaOH (0.04 eq), RT, 30 min; ii) Ph₂O, reflux, 4 h

The choice of base, as well its exact concentration, is a very important variable in selecting for the desired calix[*n*]arene. The yield of calix[4]arene is at an optimum when there are between 0.03 and 0.04 equivalents of base – with less than 0.03 equivalents, the yield decreases drastically,

and with more than 0.04 equivalents, calix[6]arene is more selectively formed.⁵ The cation associated with the base also has a small but significant effect on the reaction, with sodium hydroxide being preferred for the selective synthesis of calix[4]arene above the other alkali metals.⁵

Cyclisation to form the calix[4]arene can follow two pathways. Under mild conditions, the calix[8]arene is formed as the product of kinetic control. This happens as a pair of linear tetramers associate to form a hemicalix[8]arene, which extrudes a water molecule at each end to form the cyclic octamer. The cyclic tetramer, however, is a product of thermodynamic control and thus requires harsher conditions – i.e. refluxing at 260 °C. This product can form either by the direct cyclisation of the linear tetramer in the pseudocalix[4]arene conformation, or by molecular mitosis of the calix[8]arene.⁵ When a reaction failed to heat to the desired reflux temperature, instead only reaching 170 °C, the product formed was confirmed by mass spectrometry to be *p*-*tert*-butylcalix[8]arene. Heating this product in refluxing diphenyl ether for 4 hours yielded the cyclic tetramer, confirming the pathway of molecular mitosis.

The ¹H NMR spectrum (Figure 2.3) reveals a great deal of information about the conformation of the molecule. Despite the molecule's large size, the ¹H NMR spectrum is rather simple as a result of the C₄ symmetry.^{8,9} There are four regions in the spectrum associated with each of the four proton types: the *t*-butyl protons, the methylene bridge protons, the aromatic protons and the phenolic protons.

Due to the symmetry of the molecule, the *t*-butyl protons, the aromatic protons and the phenolic protons all appear as singlets. The sharp singlet at 10.4 ppm shows the strong hydrogen bonding between the phenolic protons.

At room temperature, the methylene protons are represented by two broad signals. This is as a result of the conformational flexibility of the calix[4]arene. Upon cooling to 0 °C (Figure 2.3), these signals resolve into distinct doublets. The two signals correspond to the axial and equatorial positions these protons can reside in. The axial protons are in the same plane as the aromatic rings and are consequently less shielded and are assigned to the more downfield signal (4.3 ppm). The equatorial protons are relatively more shielded by the electron clouds of the aromatic rings, and appear more upfield at 3.5 ppm.¹⁰

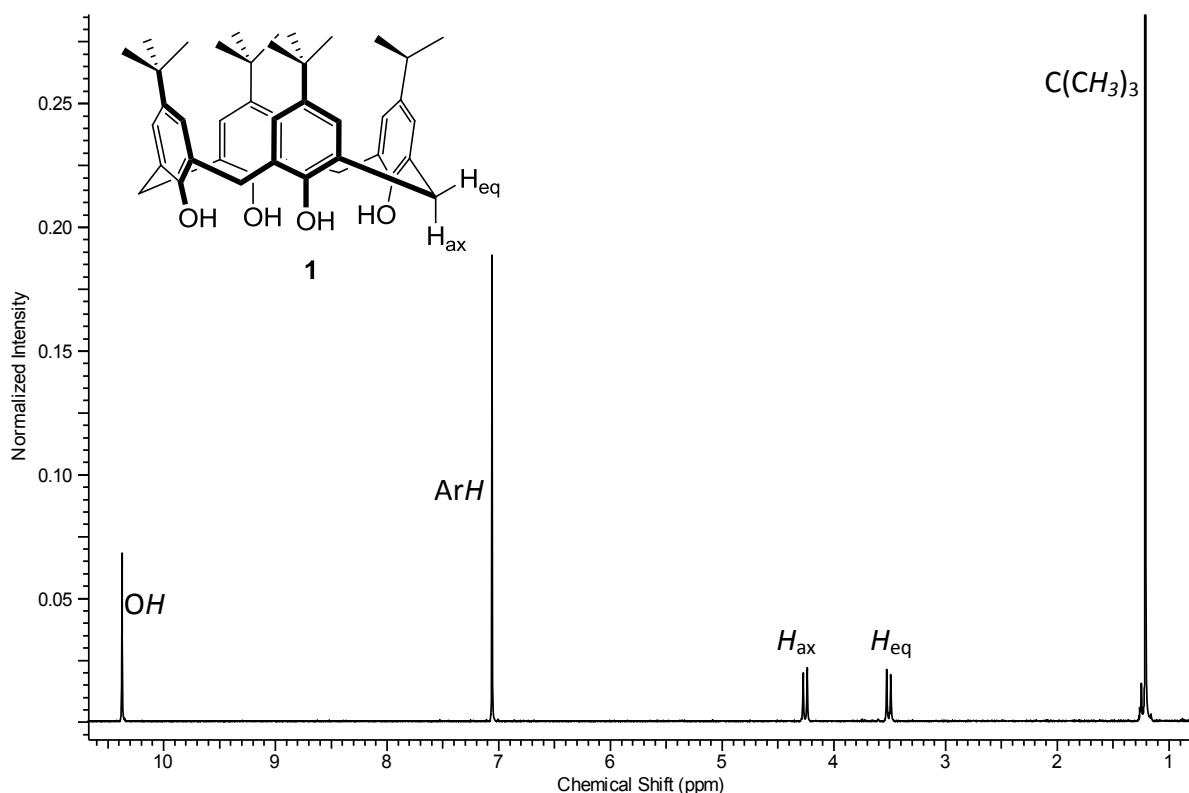


Figure 2.3: ^1H NMR spectrum of calix[4]arene **1** (obtained at 0 °C)

2.3. Synthesis of Non-Butylated Calix[4]arene Oxazoline

Debutylation of the calix[4]arene was achieved by a reverse Friedel-Crafts reaction.¹¹ Calix[4]arene **1** was dissolved in dry toluene and phenol was added under stirring. After 10 minutes, aluminium trichloride was added quickly and the mixture stirred vigorously for 2 hours (Figure 2.4). Purification could be achieved by trituration from diethyl ether to yield the product **2** as a white powder in 67% yield – allowing the reaction to be performed easily on large scale.

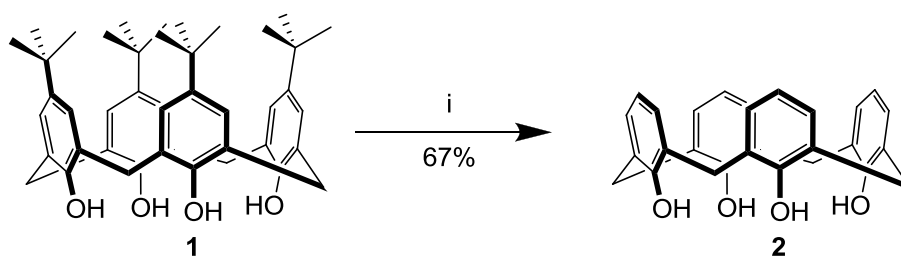


Figure 2.4: Synthesis of debutylated calix[4]arene **2**. i) AlCl_3 (4.8 eq), PhOH (1.2 eq), toluene, RT, 2 h

As discussed in Chapter 1, calix[4]arene requires a minimum of a three-carbon chain at the phenolic positions to be conformationally stable.⁵ The calix[4]arene was consequently tetrapropylated using 1-iodopropane, with sodium hydride as base (Figure 2.5). Trituration with acid followed by crystallisation from methanol afforded the product in high purity, again allowing gram scale reactions.¹²

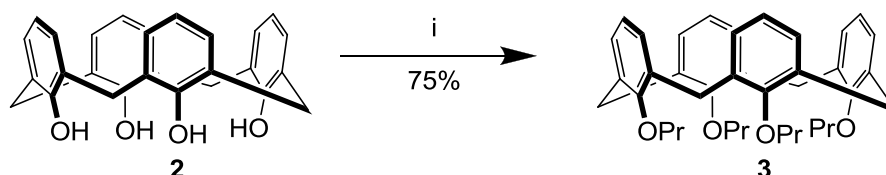


Figure 2.5: Tetrapropylation to give calix[4]arene **3**. i) NaH (17 eq), 1-iodopropane (10 eq), DMF, RT, 12 h

The ^1H NMR spectrum of **3** (Figure 2.6) allows us to define a new region – that of the propyl groups. For this symmetrical molecule, the identical propyl groups contribute three signals. As expected, the terminal CH_3 protons appear as a fairly upfield triplet, while the protons of the $-\text{CH}_2-$ group are indicated by a multiplet signal at 1.95 ppm. The protons of the $-\text{OCH}_2-$ moiety display their signal as a triplet between the doublets for the methylene bridges. The aromatic region is also more complex than for the parent calix[4]arene **1** as a result of the removal of the *t*-butyl groups.

Mono-functionalisation of the propylated calix[4]arene **3** could now be achieved by bromination with *N*-bromosuccinimide (NBS), using a procedure described by Gutsche.¹¹ Exactly one equivalent of freshly recrystallised NBS was used to minimise the formation of the unwanted dibromo calix[4]arene. Bromo calix[4]arene **4** was subjected to careful and thorough drying under vacuum before being subjected to a lithium-halogen exchange with *n*-BuLi (Figure 2.7). Quenching with freshly condensed, powdered CO_2 resulted in the mono-acid **5**, which could be purified by column chromatography and isolated in reasonable yield (73% over two steps).

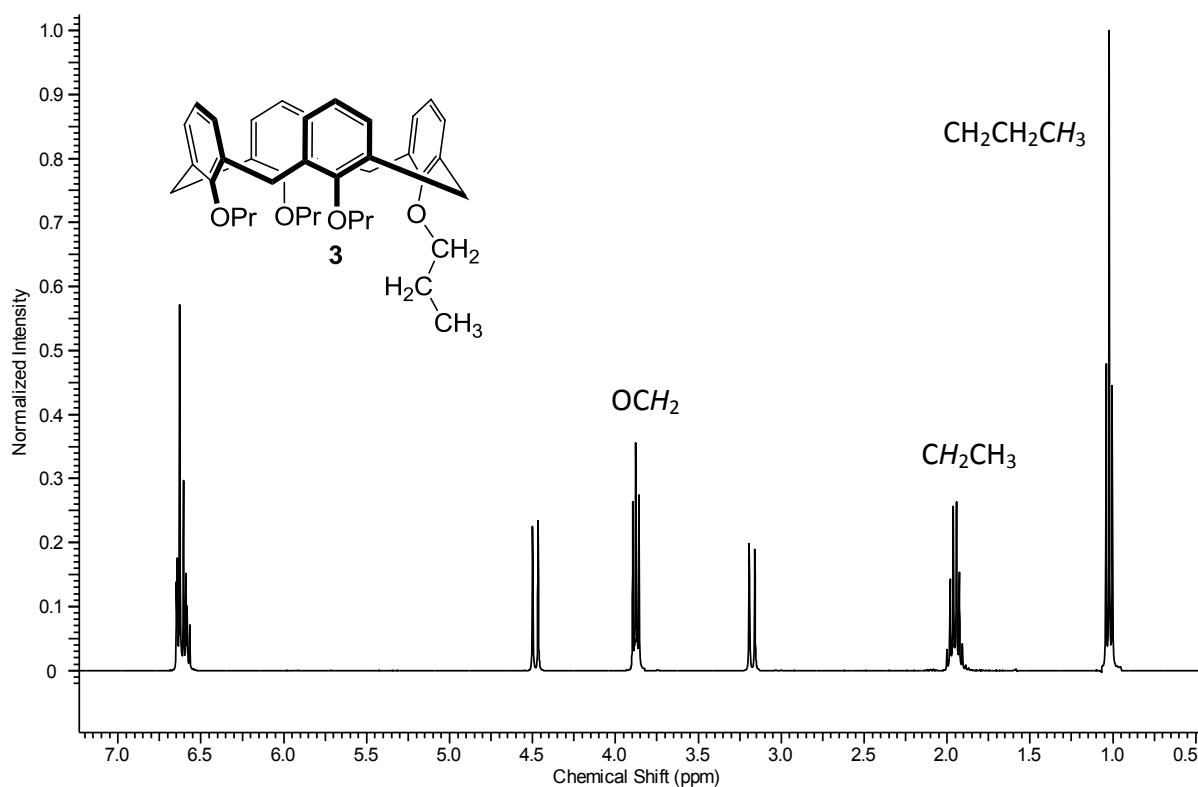


Figure 2.6: ^1H NMR spectrum of propylated Calix[4]arene **3**

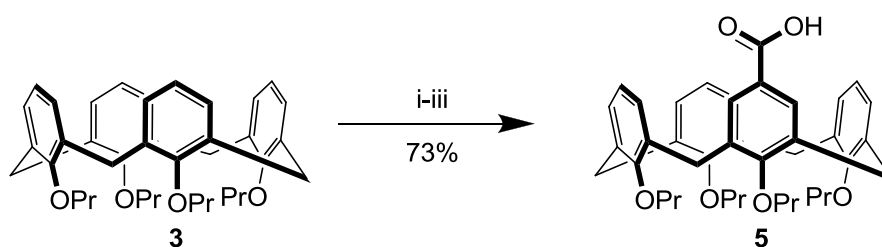


Figure 2.7: Lithium-bromine exchange yielding carboxylic acid **5**. i) NBS (1.0 eq), MEK, RT, 18 h; ii) $n\text{-BuLi}$ (2 eq), NaH (0.2 eq), THF, -78°C , 30 min; iii) CO_2 (s)

The ^1H NMR spectrum of **5** reveals the loss of symmetry in the molecule (Figure 2.8). The calix[4]arene is now in the pinch cone conformation. The aromatic region is significantly more complex than for the precursor calix[4]arenes. The remaining regions are also more complex, as the resonances for the no-longer equivalent propyl and bridging protons overlap.

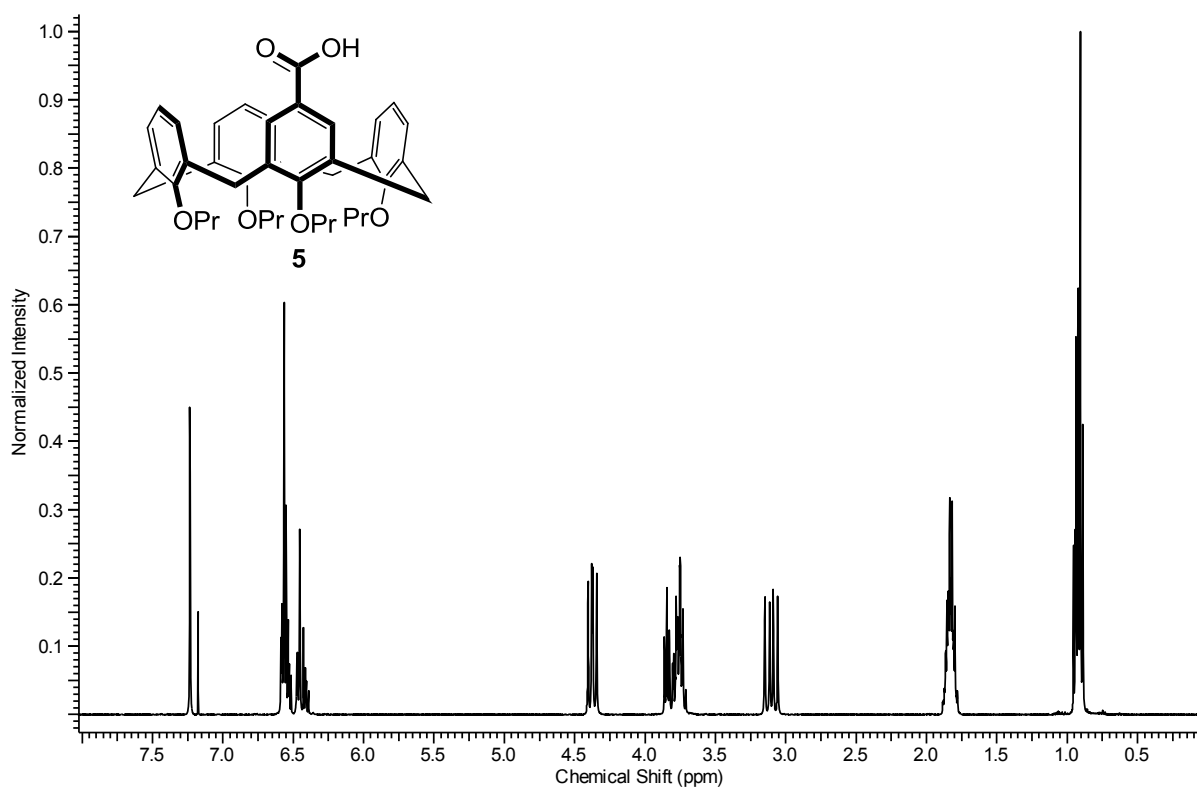


Figure 2.8: ^1H NMR spectrum of carboxy calix[4]arene **5**

The oxazoline could be generated through the formation of the amide with a chiral amino alcohol, followed by ring closing.² To evaluate the effect of steric bulk on the outcome of asymmetric catalysis, it was decided to make two different oxazolines, featuring either an isopropyl or a *t*-butyl R-group.

Reacting the carboxylic acid with oxalyl chloride converted it to the acid chloride. The acid chloride was then inertly transferred to a solution of either (*S*)-2-amino-3-methylbutan-1-ol (*L*-valinol) or (*S*)-2-amino-3,3-dimethylbutan-1-ol (*L-tert*-leucinol). After complete conversion to the amide was visible on TLC, mesyl chloride was added to the solution to facilitate ring closure. The desired oxazolines were isolated in good yields (Figure 2.9 and Figure 2.10).

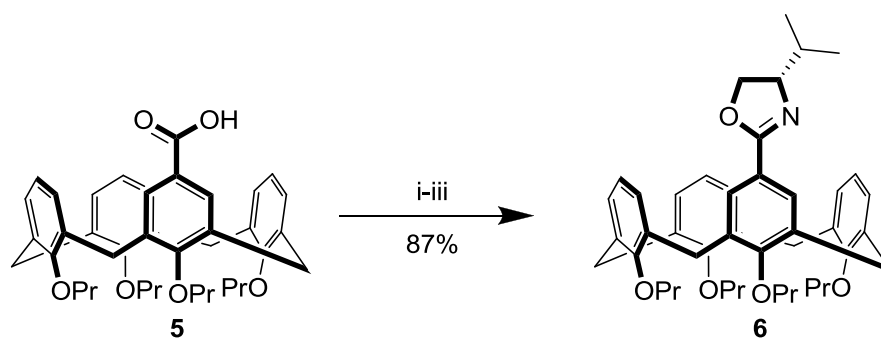


Figure 2.9: Formation of isopropyl oxazoline calix[4]arene **6**. i) (COCl)₂ (5 eq), RT, 24 h; ii) Et₃N (3 eq), L-valinol (1.3 eq), DCM, 0 °C to RT, 24 h; iii) MsCl (6 eq), DCM, RT, 24 h

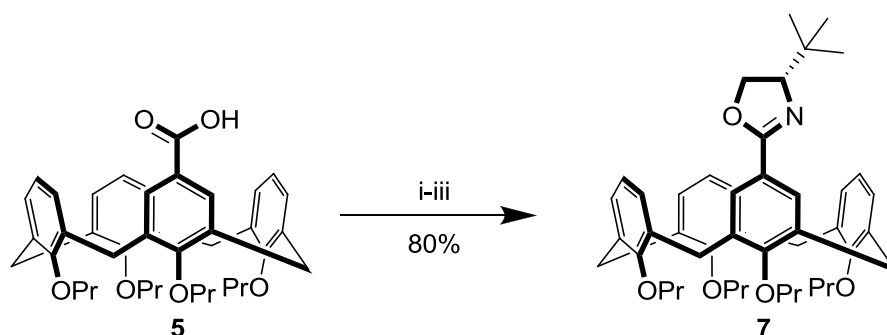


Figure 2.10: Formation of *tert*-butyl oxazoline calix[4]arene **7**. i) (COCl)₂ (3 eq), RT, 3 h; ii) Et₃N (6 eq), L-*tert*-leucinol (1.2 eq), DCM, 0 °C to RT, 18 h; iii) MsCl (3 eq), DCM, RT, 3 h

Examination of the ¹H NMR spectrum of the oxazolines allows for confirmation of their structure. As a representative example, the ¹H NMR spectrum of **6** (Figure 2.11) shows the signals corresponding to the isopropyl group, as well as the protons of the oxazoline ring. Importantly, there are no signals for the amide intermediate.

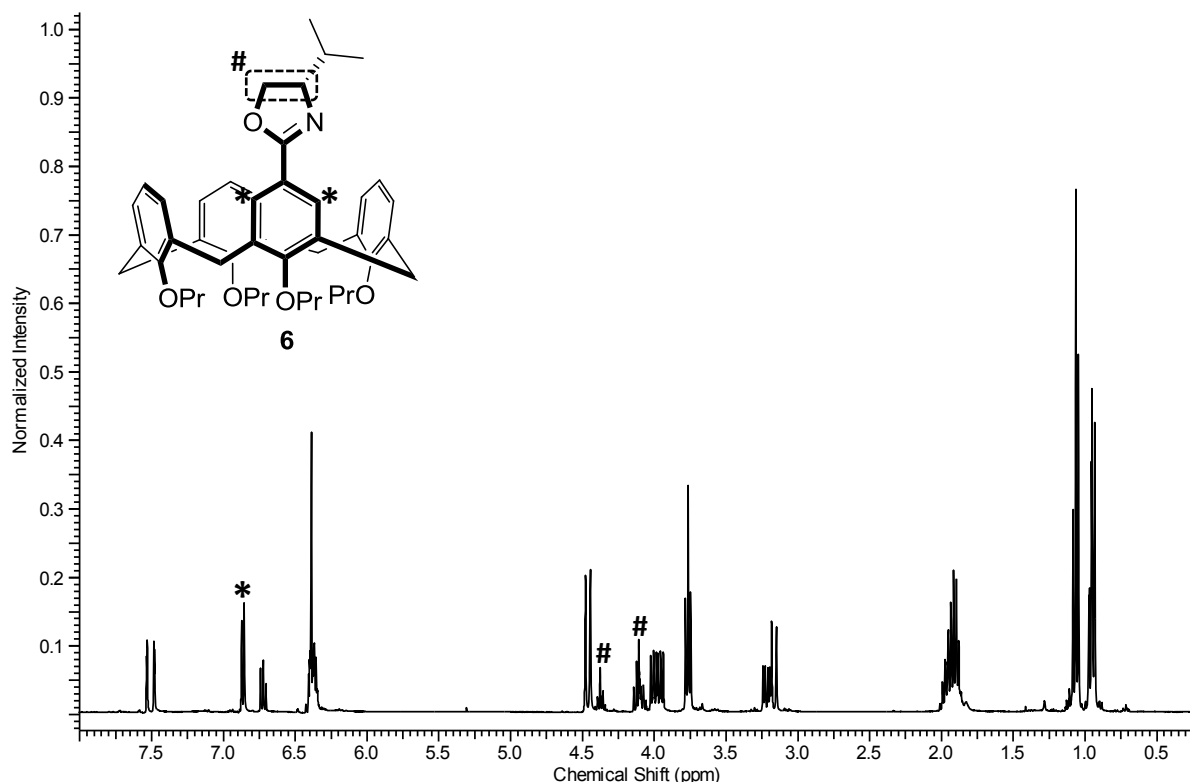


Figure 2.11: ^1H NMR spectrum of isopropyl oxazoline **6**

2.4. Synthesis of Butylated Calix[4]arene Oxazoline

For the synthesis of the butylated calixarenes from the parent calix[4]arene, mono-functionalisation needed to be achieved. The first step towards this involved selective tripropylation of the lower rim. The triprotection was achieved by following a procedure developed by Shinkai *et al.*¹³ A mixture of barium oxide and barium hydroxide octahydrate was added to **1** together with a large excess of 1-iodopropane (Figure 2.12). The exact mechanism of this unusual combination of bases is unknown – what is known, however, is that either base in isolation gives low yields of the desired tripropylated calix[4]arene **2**. The combination of BaO and Ba(OH)₂, together with the choice of alkyl halide (1-iodopropane) has been shown to be necessary for obtaining the tripropylated compound in the cone conformation. Despite the subtle effects at work and the complexity of the reaction, this reaction gave high yields of **8** with good reproducibility. The product is easily purified by recrystallisation from DCM/EtOH, allowing the reaction to be done on multi-gram scale.

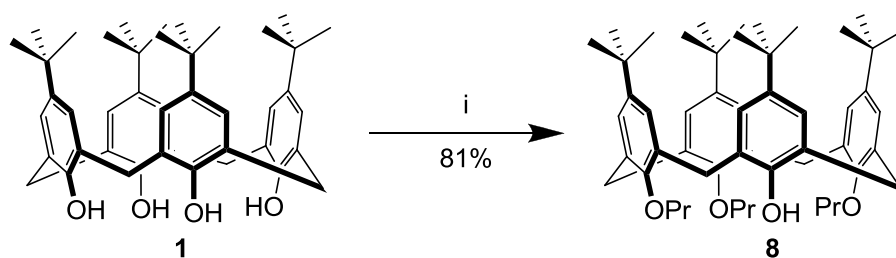


Figure 2.12: Selective tripropylation. i) BaO (3.3 eq), Ba(OH)₂·8H₂O (5.8 eq), 1-iodopropane (28 eq), DMF, RT, 2 h

An examination of the ¹H NMR spectrum of calix[4]arene **8** showed that there has been a loss of symmetry from C₄ to C_v. The calix[4]arene now assumes a pinch cone conformation. This change in conformation is associated with an increase in the separation of the signals of the axial and equatorial methylene bridge protons. Importantly, the alkylation of the lower rim destroys the strong hydrogen bonding between the phenolic protons. The remaining phenolic residue, now unable to undergo hydrogen bonding, has shifted from 10.35 ppm to 5.58 ppm.

Mono-functionalisation could now be realised by taking advantage of the differing reactivity rates of the unprotected versus protected aromatic rings.¹⁴ Nitration through an *ipso*-substitution pathway was performed, using concentrated nitric acid and acetic acid to generate the nitronium ion (Figure 2.13).¹⁵ This reaction takes place in the order of minutes, with the rate of reaction increasing as the reaction progresses, so the solution needs to be carefully monitored by TLC. The solution was quenched by pouring into water after approximately 11 minutes. Despite the difficulty in controlling the reaction, reasonably good yields of nitro calix[4]arene **9** could be isolated.

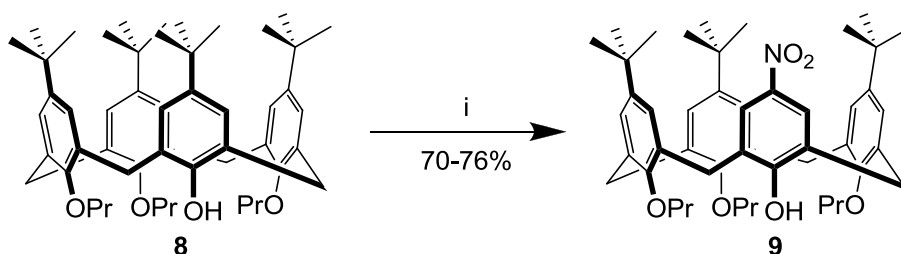


Figure 2.13: Synthesis of nitro calix[4]arene **9**. i) 65% HNO₃ (7.2 eq), AcOH, DCM, 0 °C to RT, 10-12 min

Inspection of the ^1H NMR spectrum of **9** reveals that the calix[4]arene is in the pinch cone conformation. The nitrated ring and its opposite aromatic ring lie outwards, with the remaining two rings upright. This information is revealed by the chemical shift of the signals of the *t*-butyl groups as a result of anisotropic effects. The upright rings experience shielding from the two outer-facing rings. It is thought that this conformation arises as a result of the smaller bulk of the phenolic moiety relative to the propylated positions.

To ensure conformational stability of the calix[4]arene, the remaining phenolic position needed to be propylated. This reaction proceeded remarkably slowly, requiring refluxing in acetonitrile with a large excess of 1-iodopropane for two complete days before starting material could no longer be detected by TLC (Figure 2.14). When evaluating the ^1H NMR spectrum of **10** (Figure 2.15), it appears that the molecule has changed conformations, with the nitro ring and its opposite partner facing inwards and the remaining rings lying outward. With all four lower rim positions identical, it seems that this conformation is now the result of the small nitro group relative to a *tert*-butyl group.

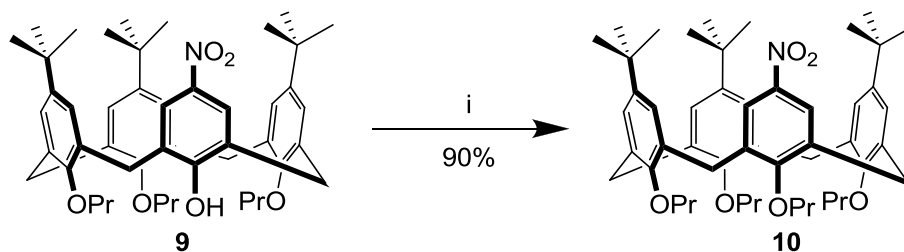


Figure 2.14: Propylation of the final phenolic position. i) Na_2CO_3 (3 eq), 1-iodopropane (18 eq), MeCN, reflux, 48 h

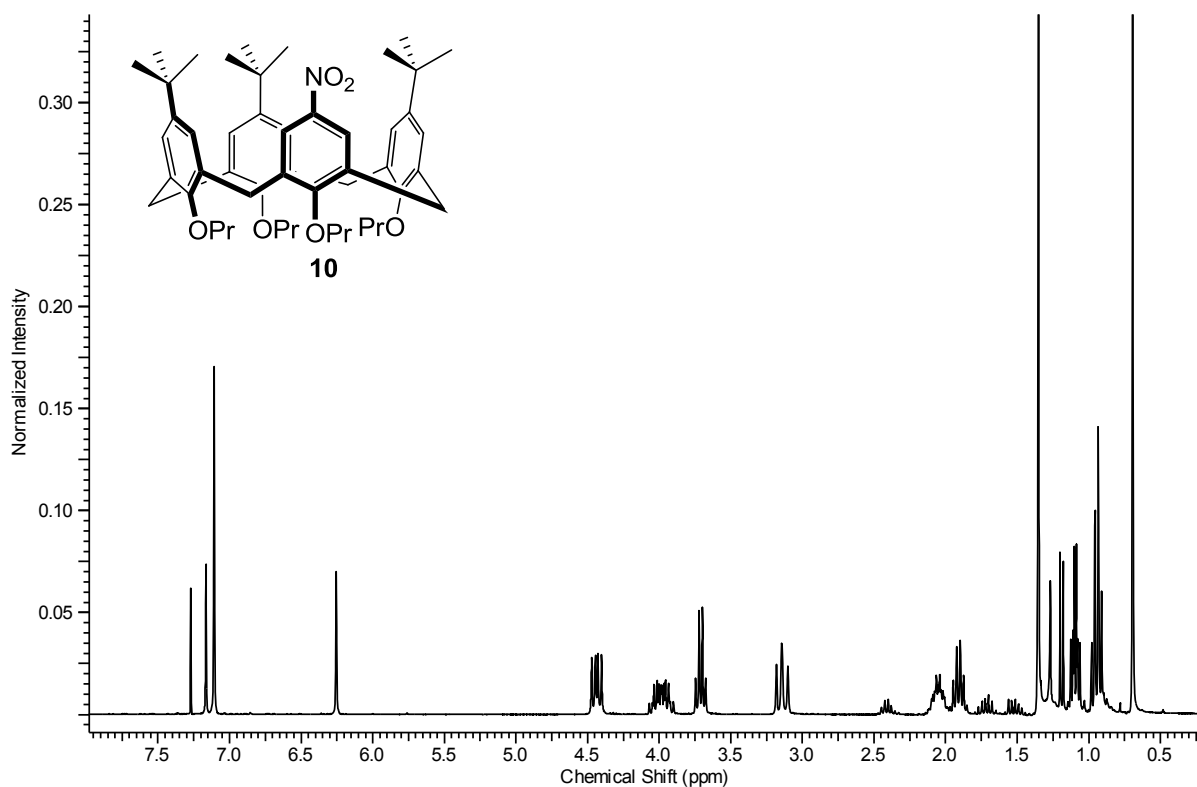


Figure 2.15: ^1H NMR spectrum of nitro calix[4]arene **10**

With the nitro calix[4]arene in hand, reduction to form the amine **11** could be performed with palladium on charcoal and hydrazine hydrate (Figure 2.16).¹⁶ This reaction reproducibly gave yields in excess of 90%. Purification of the amine could be achieved by recrystallisation from DCM/EtOH. The ^1H NMR spectrum of **11** revealed that the calix[4]arene was in a similar pinch cone conformation to **10**.

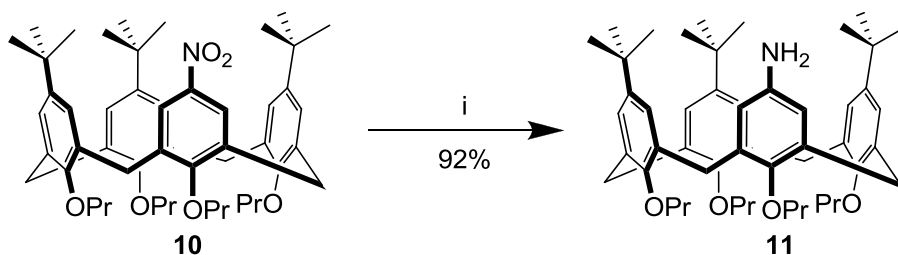


Figure 2.16: Synthesis of amino calix[4]arene **11**. i) Pd/C (10 mol %), H₂NNH₂ (2.6 eq), EtOH, reflux, 1.5 h

The conversion of the amino calix[4]arene **11** to iodo calix[4]arene **12** was performed using a one-pot protocol as described by Knochel and co-workers for the iodination of aryl amines.¹⁷ Potassium iodide, sodium nitrite and *p*-toluenesulfonic acid were added to a solution of **11** (Figure 2.17), which was stirred at room temperature for 90 minutes to form iodo calix[4]arene **12**, which could be rapidly crystallised from DCM/EtOH (solvate with DCM: **12**, 0.5 : 1). ¹H NMR spectral analysis revealed that the iodo calix[4]arene was in the same pinch cone conformation as its amino and nitro precursors. An impurity that persistently co-crystallises with **12**, as well as co-eluting in column chromatography, is the protonated by-product (that is, a proton in the position occupied by iodine in **12**).

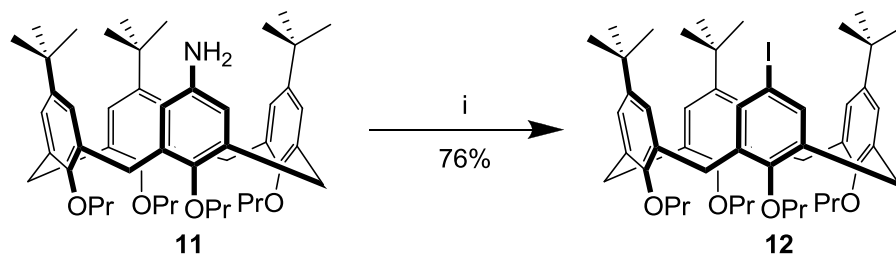


Figure 2.17: Conversion to iodo calix[4]arene **12**. i) TsOH (3 eq), NaNO₂ (2.5 eq), KI (3 eq), MeCN, RT, 1.5 h

The ¹H NMR spectrum of the DCM: **12** solvate displays some noteworthy characteristics (Figure 2.18). Firstly, one can see that the signals for the axial (doublets at 4.37 and 4.44 ppm) and equatorial protons (doublets at 3.07 and 3.15 ppm) have shifted further apart than for the parent *tert*-butylcalix[4]arene, as well as having more complex chemical shift patterns as a result of the reduction in symmetry. Secondly, the signals for the aromatic protons show the more complex pattern of a monofunctionalised system. Finally, the relative chemical shifts of the now non-equivalent *t*-butyl groups allow us to determine the conformation of the calix[4]arene. Close inspection reveals the small amount of protonated calix[4]arene (I = H) which is present but currently inseparable.

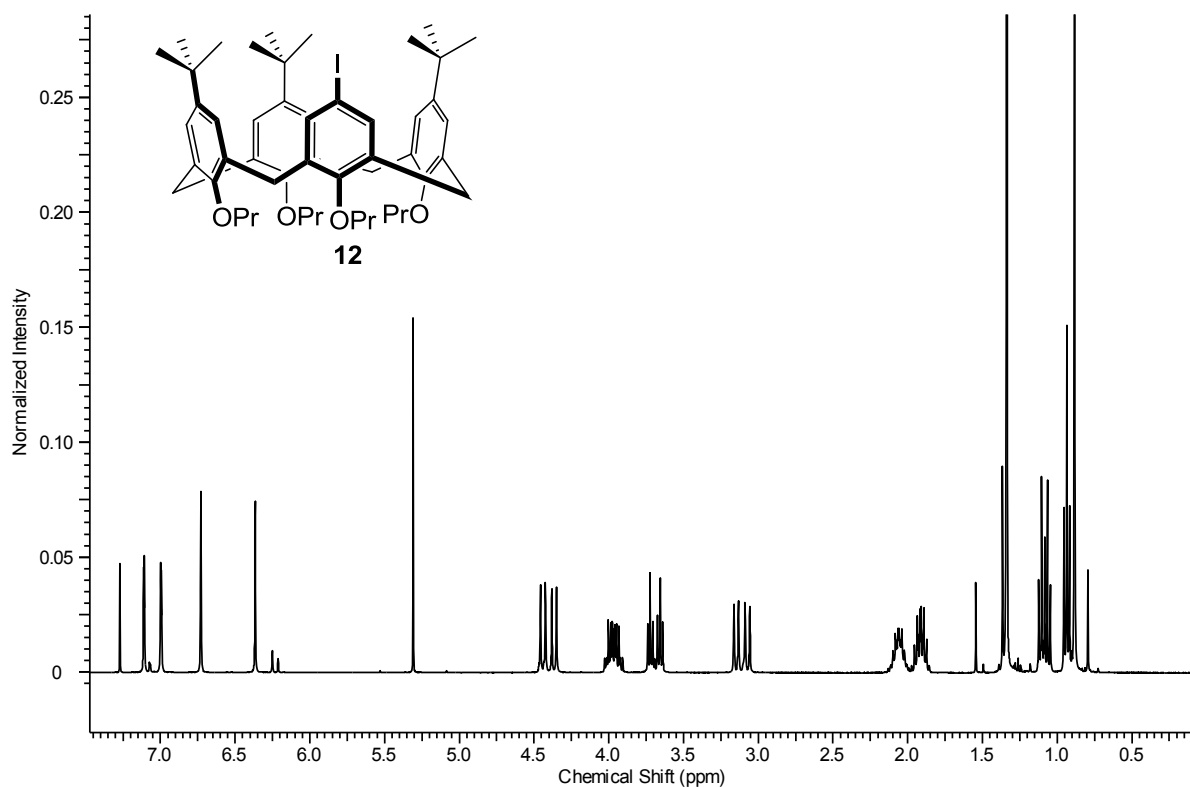


Figure 2.18: ^1H NMR spectrum of Iodo Calix[4]arene **12**

Iodo calix[4]arene **12** was subsequently subjected to magnesium-iodine exchange using *i*-PrMg·LiCl₂.¹ After stirring the THF solution for two hours at room temperature, exchange had taken place. Quenching with freshly condensed powdered CO₂ resulted in the desired carboxylic acid **13** in 60% yield (Figure 2.19). Experiments in our group have shown that conventional lithium-halogen exchange with alkyl lithiums is not effective on the iodinated calix[4]arene, giving low yields of the desired acid with significant proportions of the protonated by-product.¹

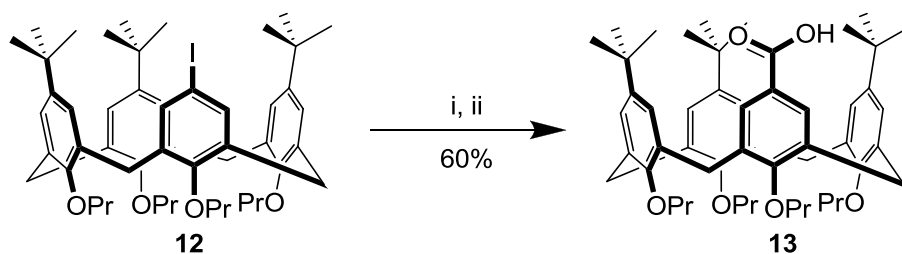


Figure 2.19: Formation of carboxylic acid **13**. i) *i*-PrMg·LiCl₂, THF, 0 °C to RT, 1.5 h; ii) CO₂ (s)

Oxazoline formation was then performed in a similar manner to that used for the debutylated analogue.¹ The acid chloride was formed with the use of freshly distilled thionyl chloride under reflux. Thereafter, the excess thionyl chloride was removed under inert conditions and the residue re-dissolved in dry solvent. The solution was slowly added to a stirring solution of an amino alcohol - either L-valinol (Figure 2.20) or L-*tert*-leucinol (Figure 2.21) - and triethylamine. After stirring overnight, the solution was worked up, and the residue of the organic layer transferred to a clean flask. This solid was taken up in dry DCM and reacted with thionyl chloride, which facilitated the cyclisation to the oxazoline.

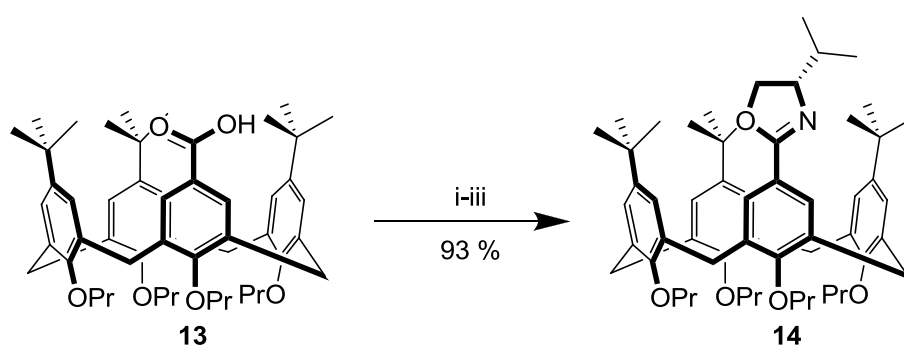


Figure 2.20: Formation of isopropyl oxazoline **14**. i) SOCl_2 (36 eq), reflux, 1.75 h; ii) L-valinol (1.5 eq), Et_3N (4.7 eq), DCM, 0 °C - RT, 18 h; iii) SOCl_2 (14 eq), DCM, RT, 12 h

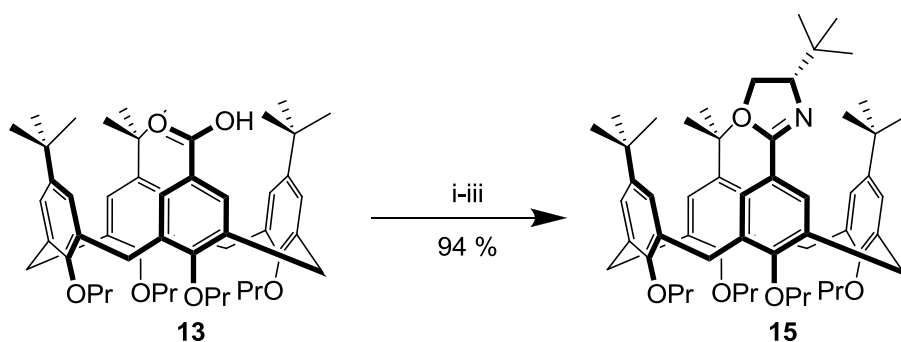


Figure 2.21: Formation of *tert*-butyl oxazoline **15**. i) SOCl_2 (60 eq), reflux, 1.75 h; ii) L-*tert*-leucinol (1. eq), Et_3N (3.6 eq), DCM, 0 °C - RT, 18 h; iii) SOCl_2 (14 eq), DCM, RT, 12 h

The ^1H NMR spectrum of the oxazolines (for example, that of isopropyl oxazoline **14** as seen in Figure 2.22) confirms their formation, displaying the addition of the three oxazoline protons in the region

between 3.67 – 3.83 ppm, while lacking the signal for the NH that would be present in the intermediate amide product (at 5.81 ppm).

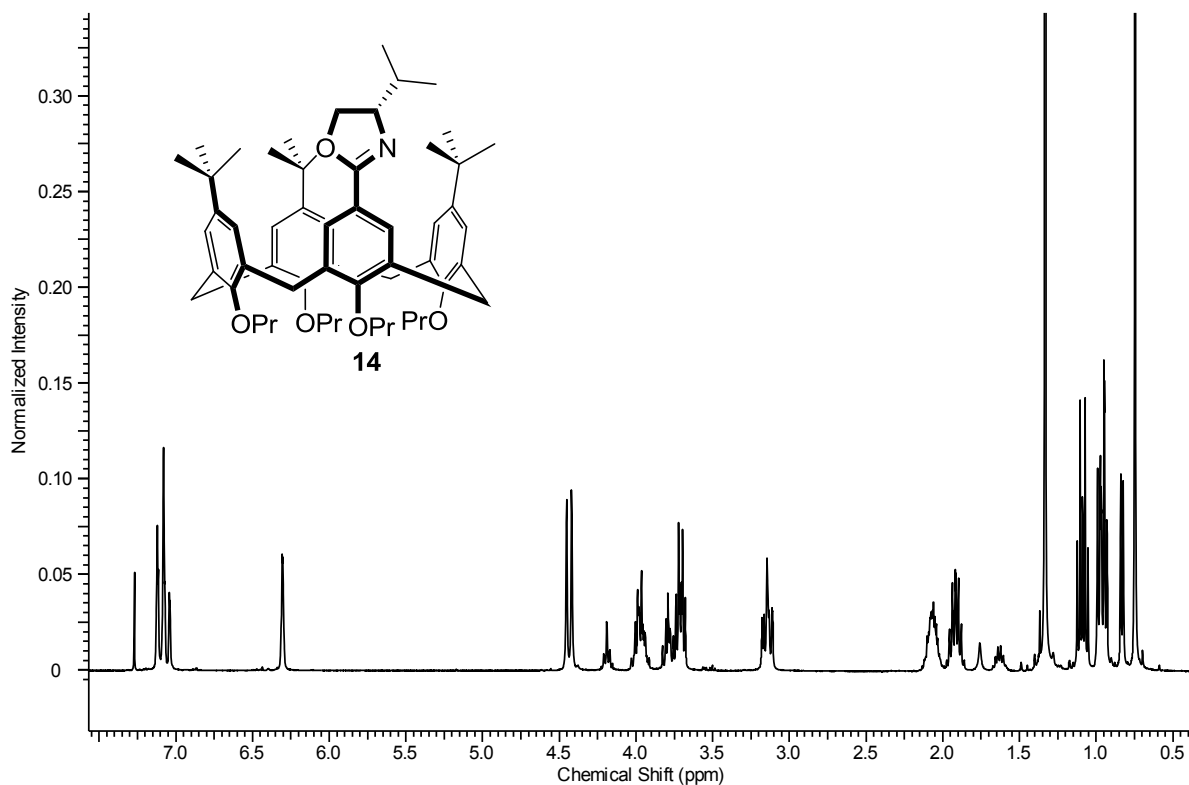


Figure 2.22: ^1H NMR spectrum of isopropyl oxazoline **14**

2.5. Ortholithiation Steps towards Inherent Chirality

With the desired oxazolines in hand, ortholithiation to yield the thioether ligands could be performed. The diastereoselective ortholithiation methodology developed by Arnott and Herbert was followed.^{1,2} Diastereoselectivity results from careful selection of the alkyl lithium, additive and solvent.

The debutylated isopropyl oxazoline calix[4]arene **6** was dried and dissolved in dry pentane in an oven-dried Schlenk flask, together with tetramethylethylenediamine (TMEDA). The flask was cooled to $-78\text{ }^\circ\text{C}$ and *c*-PentLi was slowly added. The sealed flask was stirred at $-78\text{ }^\circ\text{C}$ for 5 hours. Thereafter, the solution was quenched with dimethyl disulfide and the flask allowed to warm to room temperature for a further 12 hours (Figure 2.23). The yield was determined by ^1H NMR to be 93%. The use of TMEDA as ligand produces the (*cR*) diastereomer **16-A** (94% de).²

Diastereoselectivity could be determined through careful integration of the ^1H NMR signals for the methyl thioether protons: the (*cR*) diastereomer's signal appears at 7.35 ppm, with that of the (*cS*) at 7.33 ppm.[†] Spinworks software was used to perform necessary deconvolution.

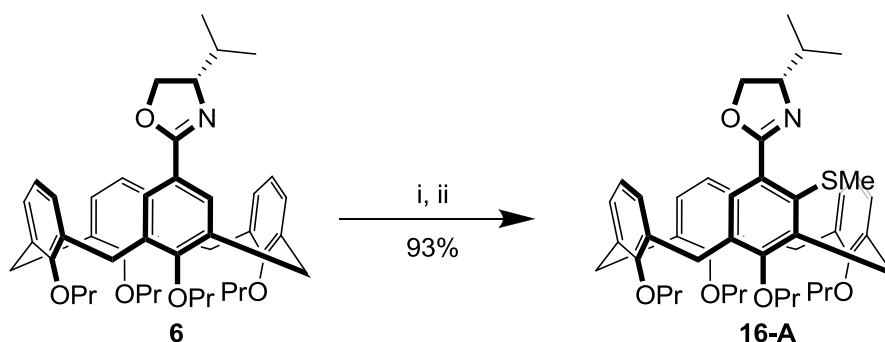


Figure 2.23: Ortholithiation to form ligand **16-A**. i) *c*-PentLi (5 eq), TMEDA, (10 eq), pentane, $-78\text{ }^{\circ}\text{C}$, 5 h;
ii) Me_2S_2 (10 eq), $-78\text{ }^{\circ}\text{C}$ to RT, 12 h

The (*cS*) diastereomer can be synthesised through an analogous procedure, with the use of di-*tert*-butyldiglyme as ligand (replacing TMEDA) and *s*-BuLi as the lithiating reagent (Figure 2.24). The choice of ligand is crucial in obtaining the desired diastereomer.² The thioether **16-B** was synthesised in 95% yield, with a diastereomeric excess (de) of 92% (as determined by ^1H NMR).[‡]

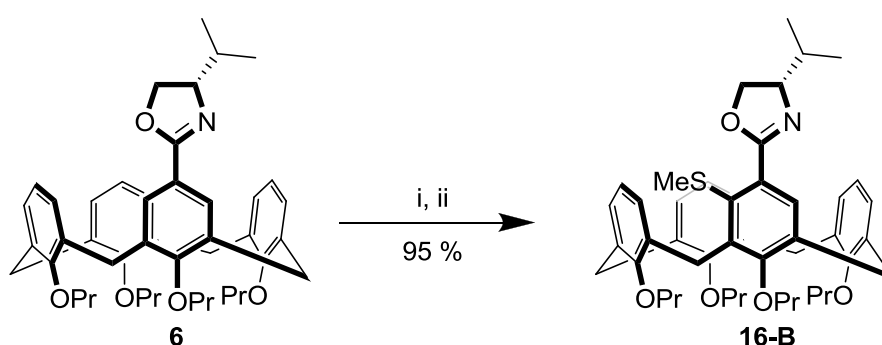


Figure 2.24: Ortholithiation to form ligand **16-B**. i) *s*-BuLi (5 eq), TMEDA, (10 eq), pentane, $-78\text{ }^{\circ}\text{C}$, 5 h;
ii) Me_2S_2 (10 eq), $-78\text{ }^{\circ}\text{C}$ to RT, 12 h

[†] An explanation for the classification of inherently chiral calixarenes as (*cR*) or (*cS*) can be found in Appendix III.

[‡] This compound was synthesised by Simon Herbert.

The debutylated *tert*-butyl oxazoline was targeted next for ortholithiation. The use of *s*-BuLi and TMEDA produced the (*cR*) diastereomer **17-A** in both excellent yield (95%) and diastereoselectivity (>99% de) (Figure 2.25).¹⁸

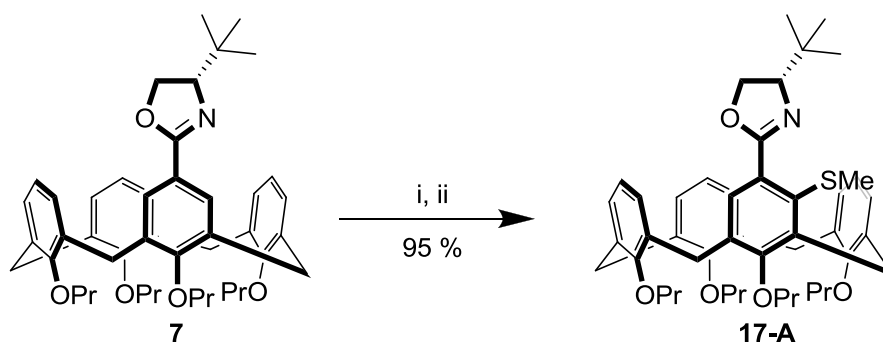


Figure 2.25: Ortholithiation to form ligand **17-A**. i) *s*-BuLi (5 eq), TMEDA, (10 eq), pentane, $-78\text{ }^{\circ}\text{C}$, 5 h;
ii) Me_2S_2 (10 eq), $-78\text{ }^{\circ}\text{C}$ to RT, 12 h

The (*cS*) diastereomer was synthesised through an analogous procedure, through the use of *t*-BuLi and TMEDA, with diethyl ether as solvent (Figure 2.26). These conditions produced ligand **17-B** in 75% yield and 92% de.¹⁸

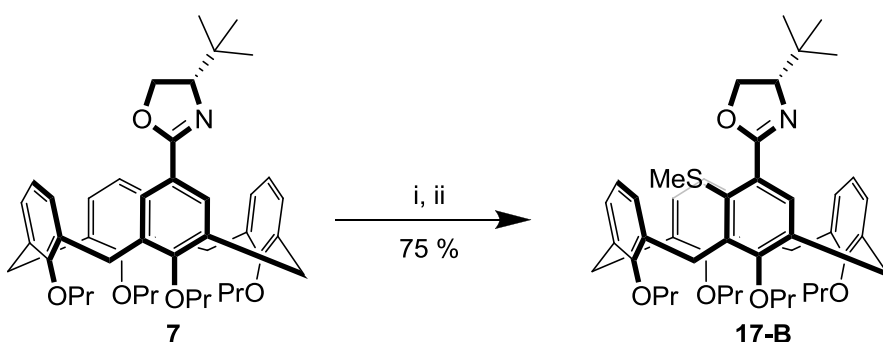


Figure 2.26: Ortholithiation to form ligand **17-B**. i) *t*-BuLi (5 eq), TMEDA, (10 eq), Et_2O , $-78\text{ }^{\circ}\text{C}$, 20 h;
ii) Me_2S_2 (10 eq), $-78\text{ }^{\circ}\text{C}$ to RT, 12 h

The *tert*-butyl calix[4]arenes could be ortholithiated in a similar fashion, although the presence of the *t*-butyl groups required longer lithiation timeframes in order to achieve optimum yields.

A hot, dry Schlenk flask was charged with *c*-PentLi solution and the solvent removed under reduced pressure. Separately, isopropyl oxazoline **14**, dry diethyl ether and TMEDA were added to a dry Schlenk flask and the contents cooled to 0 °C. Thereafter, the calix[4]arene solution was slowly injected into the flask containing the lithium reagent at –78 °C. The solution was stirred at –78 °C for 30 hours. Dimethyl disulfide was subsequently added and the mixture left to warm to room temperature overnight (Figure 2.27). Flash chromatography afforded the desired thioether **18-A** in 73% yield with good diastereoselectivity (93% de).¹

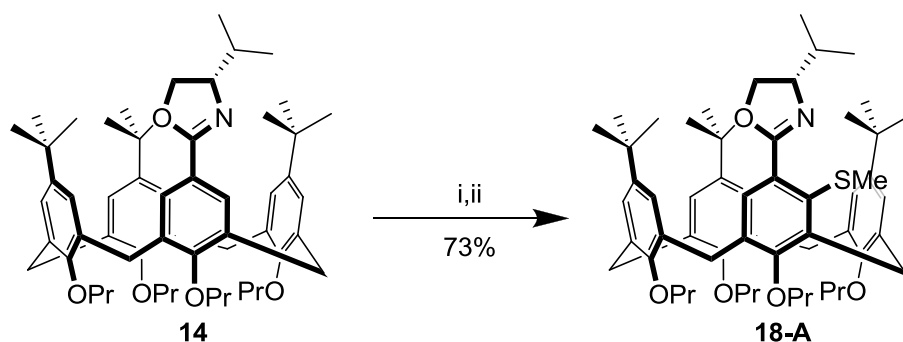


Figure 2.27: Ortholithiation to form ligand **18-A**. i) *c*-PentLi (5 eq), TMEDA, (10 eq), Et₂O, –78 °C, 30 h; ii) Me₂S₂ (10 eq), –78 °C to RT, 12 h

The (*c**S*) diastereomer, **18-B**, was not successfully isolated as attempts to reverse the selectivity were inefficient. The most successful attempt, using di-*tert*-butyldiglyme as ligand and *s*-BuLi as lithiating reagent, produced **18** in an **A**:**B** ratio of 1:1.5 (20% de). The product of this reaction was not purified or put forward for catalytic investigations as a result of the inadequate diastereomeric excess. Further studies are required to optimise this reaction.

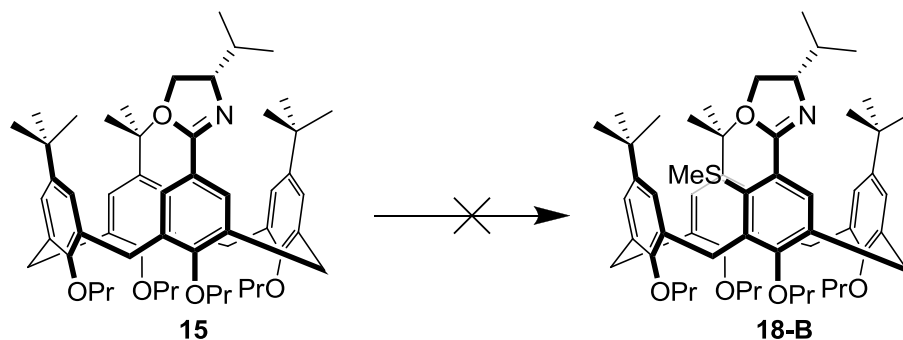


Figure 2.28: Ortholithiation to form ligand **18-B** was unsuccessful

Next, the butylated *t*-butyl oxazoline calix[4]arenes were subjected to ortholithiation. The oxazoline **15** was weighed out into an oven-dried Schlenk flask and dissolved in dry diethyl ether with TMEDA. The flask was cooled to $-78\text{ }^{\circ}\text{C}$ and *s*-BuLi was slowly added. The solution was stirred for 24 hours before being quenched with dimethyl disulfide. The mixture was allowed to warm to room temperature overnight. The thioether **19-A** was determined to be synthesised in 81% yield with >99% de (Figure 2.29).¹⁸

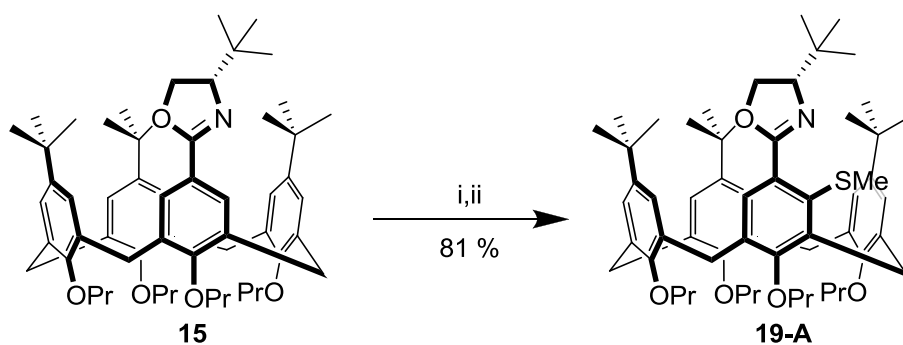


Figure 2.29: Ortholithiation to form ligand **19-A**. i) *s*-BuLi (5 eq), TMEDA (10 eq), Et₂O, $-78\text{ }^{\circ}\text{C}$, 48 h
ii) Me₂S₂ (10 eq), $-78\text{ }^{\circ}\text{C}$ to RT, 12 h

The synthesis of thioether **19-B** was somewhat less successful, requiring further optimisation studies to improve the selectivity. The isolated product was determined to be synthesised with 75% de (Figure 2.30).¹⁸

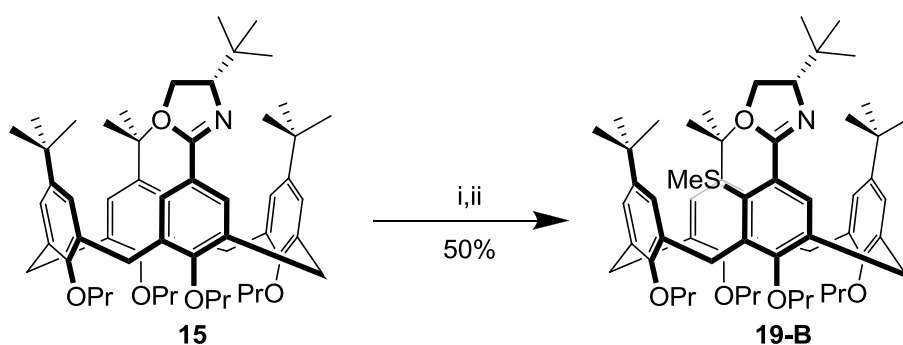


Figure 2.30: Ortholithiation to form ligand **19-B**. i) *t*-BuLi (5 eq), TMEDA (10 eq), Et₂O, $-78\text{ }^{\circ}\text{C}$, 48 h
ii) Me₂S₂ (10 eq), $-78\text{ }^{\circ}\text{C}$ to RT, 12 h

Attempts to separate the **A** and **B** diastereomers of the thioether ligands through the use of silica gel column chromatography has been unsuccessful – in all solvent systems tested to date, the two diastereomers display identical R_f values. Recrystallisation attempts have thus far also been unsuccessful. Consequently, ligands **16-A** to **19-B** were put forward to catalytic investigations in the diastereomeric ratios synthesised.

2.6. Model compounds

To evaluate the effect that the calix[4]arene bowl has when the calix[4]arenes are used as chiral ligands, a series of planar model compounds were also synthesised. Commercially available 4-iodophenol was used as starting material. The phenol group was alkylated using dimethyl sulfate to give **20** in pleasing yield. Lithium-iodine exchange was then performed with the use of *n*-BuLi, followed by quenching with solid CO_2 which yielded the carboxylic acid **21** in 71% yield (Figure 2.31).

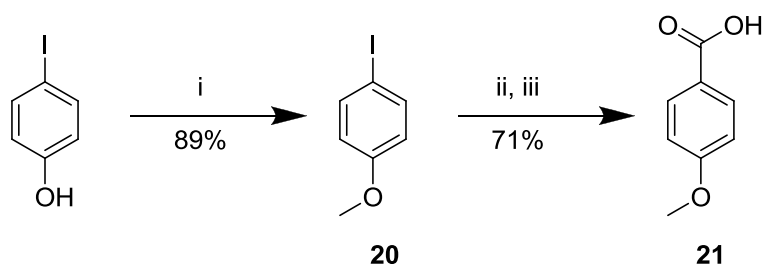


Figure 2.31: Synthesis of 4-methoxybenzoic acid. i) Na_2CO_3 (2.6 eq), Me_2SO_4 (2.9 eq), MeCN, reflux, 24 h; ii) *n*-BuLi (1.3 eq), NaH, -78°C , 15 min; iii) CO_2 (s)

The benzoic acid **21** was then converted to three different oxazolines through the use of various amino alcohols: both the *L*-valinol and *L-tert*-leucinol used on the calix[4]arenes, as well as the achiral ethanolamine (Figure 2.32). Oxalyl chloride was used to convert the carboxylic acid into the more reactive acid chloride, which was subsequently slowly injected into a stirring solution of the amino alcohol and triethylamine. After the amide had been allowed to form, mesyl chloride was added to perform the ring closing. Purification of the oxazoline was achieved through the use of silica gel chromatography, giving the oxazolines **22** - **24** in high yields.

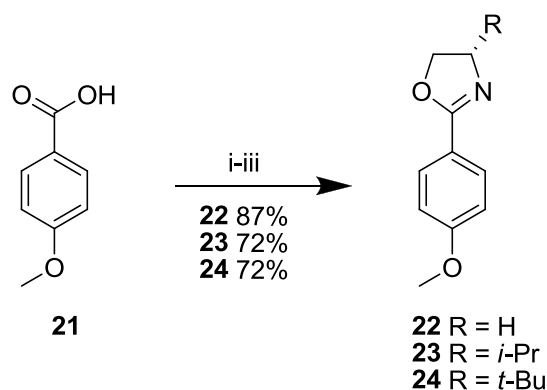


Figure 2.32: Synthesis of planar oxazolines. i) $(\text{COCl})_2$ (5 eq), DCM, RT, 12 h; ii) Et_3N , amino alcohol*, DCM, 0 °C to RT, 12 h; iii) MsCl (3 eq), RT, 12 h

***22** = ethanolamine (2.3 eq), **23** = *L*-valinol (1.2 eq), **24** = *L*-*tert*-leucinol (1.1 eq)

Prior to ortholithiation of the oxazolines **22** - **24**, the compounds were dried extensively under high vacuum. The oxazoline was then transferred to a Schlenk flask and dissolved in dry THF. *i*-PrLi was carefully added to the solution, which was then stirred for 90 minutes at -78 °C. After lithiation was complete, the solution was quenched with dimethyl disulfide (Figure 2.33). Flash chromatography yielded the pure products **25** - **27** as yellow oils in high yields.

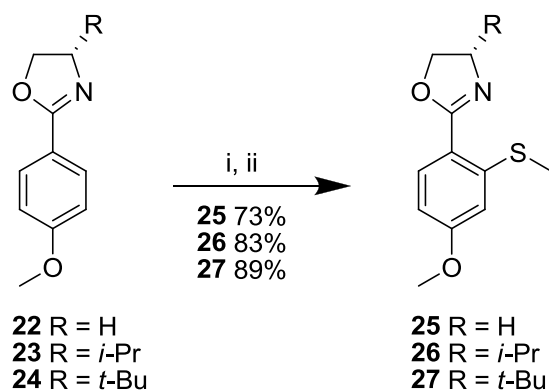


Figure 2.33: Ortholithiation to give planar model compounds **25** - **27**. i) *i*-PrLi (1.5 eq), THF, -78 °C, 1.5 h; ii) Me_2S_2 (excess), 30 min

The ^1H NMR spectrum of model compound **25** (Figure 2.34) shows a similar, but simplified, pattern to that of its calix[4]arene analogues. The methoxy protons have a singlet signal at 2.46 ppm while

those of the methyl thioether have a signal at 3.87 ppm. The protons of the oxazoline ring are represented by complex multiplets between 4.13 and 4.39 ppm. The three aromatic protons display three characteristic signals. The remaining proton *ortho* to the oxazoline ring is represented by a doublet, the furthest downfield signal at 7.83 ppm. The protons *ortho* to the methoxy functionality are more shielded as a result of the electron donating ability of the ether. The doublet of doublets at 6.66 ppm can be assigned to the proton *para* to the thioether. The doublet at 6.77 represents the proton that is *ortho* to both the methoxy and the thioether functionalities.

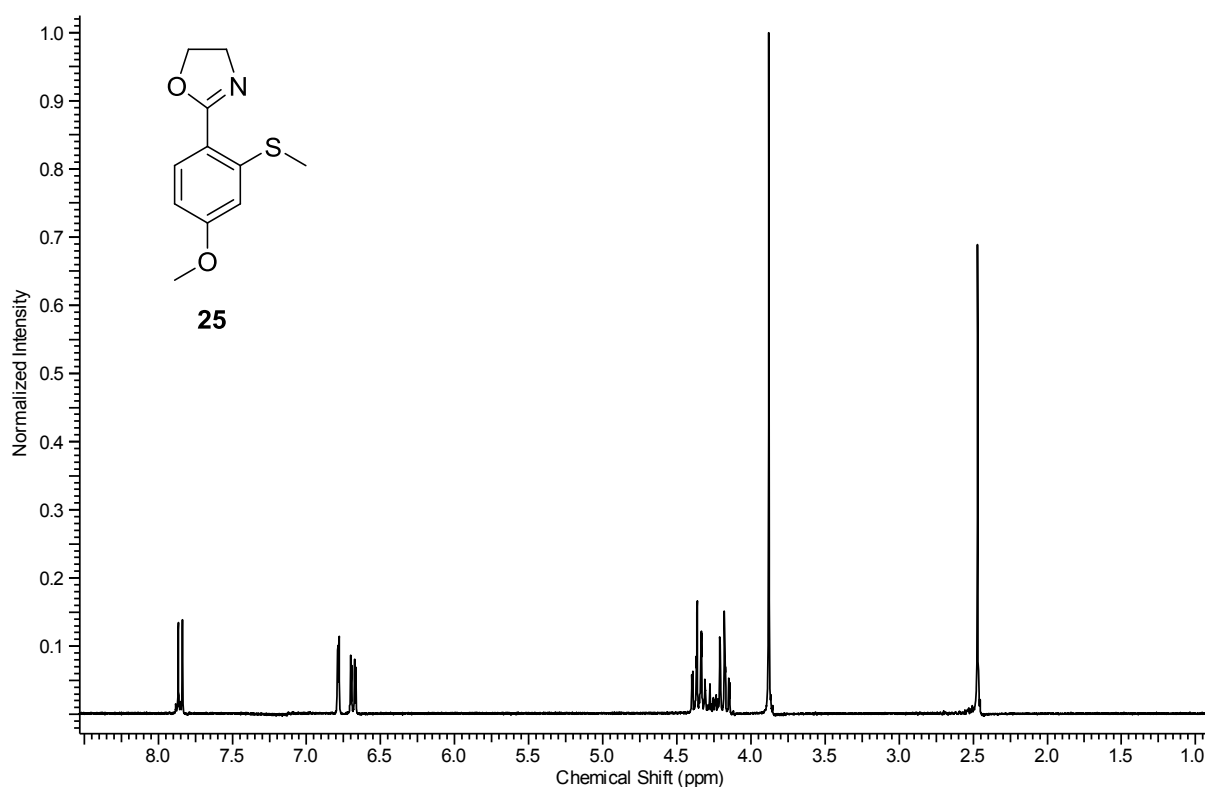


Figure 2.34: ¹H NMR spectrum of model compound **25**

2.7. References

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Chapter 3

Asymmetric Catalysis

3.1. *Palladium Catalysed Allylic Alkylation*

Based on literature precedent for bidentate thioether oxazoline ligands, it was decided to target the palladium catalysed asymmetric allylic alkylation reaction, also known as Tsuji-Trost allylation.

In the late 1960's, Tsuji showed that allyl palladium complexes would react with nucleophiles.¹ Several years later, it was shown that allylic alcohols and esters would react, in the presence of a palladium catalyst, with acetyl acetone to give the allylated product in appreciable yield.² Trost and co-workers demonstrated that π -allylpalladium complexes could be used to perform allylic alkylations with high levels of chemo-, regio- and stereoselectivity.³ Selectivity, especially stereoselectivity, is often dependant on the nature of the ligands co-ordinated to the palladium catalyst. This ability to form carbon-carbon bonds with remarkable selectivity has made metal catalysed allylic substitutions the focus of much study and several reviews have been published.⁴⁻⁶ A common reaction seen in the literature to evaluate the efficiency of the catalytic species is that of 1,3-diphenylprop-2-enyl acetate with a nucleophile generated from dimethyl malonate (Figure 3.1).

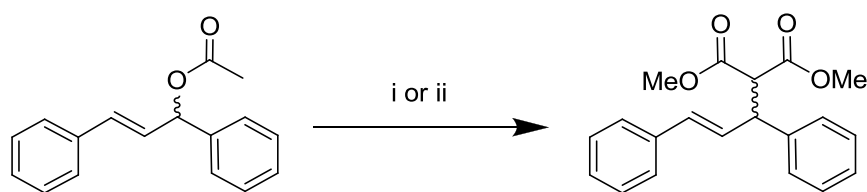


Figure 3.1: Typical test reaction. i) cat. Pd(0), NaCH(CO₂Me)₂ or ii) cat. Pd(0), CH₂(CO₂Me)₂, CH₃C(OTMS)=NTMS

The mechanism of palladium catalysed allylic substitution begins with the co-ordination of palladium(0) to the alkene (Figure 3.2).⁵ Oxidative addition of the palladium results in a η^3 -allyl complex,^{7, 8} to which nucleophilic addition can take place. Dissociation of the palladium(0) regenerates the catalytic species and releases the allylated product.⁵

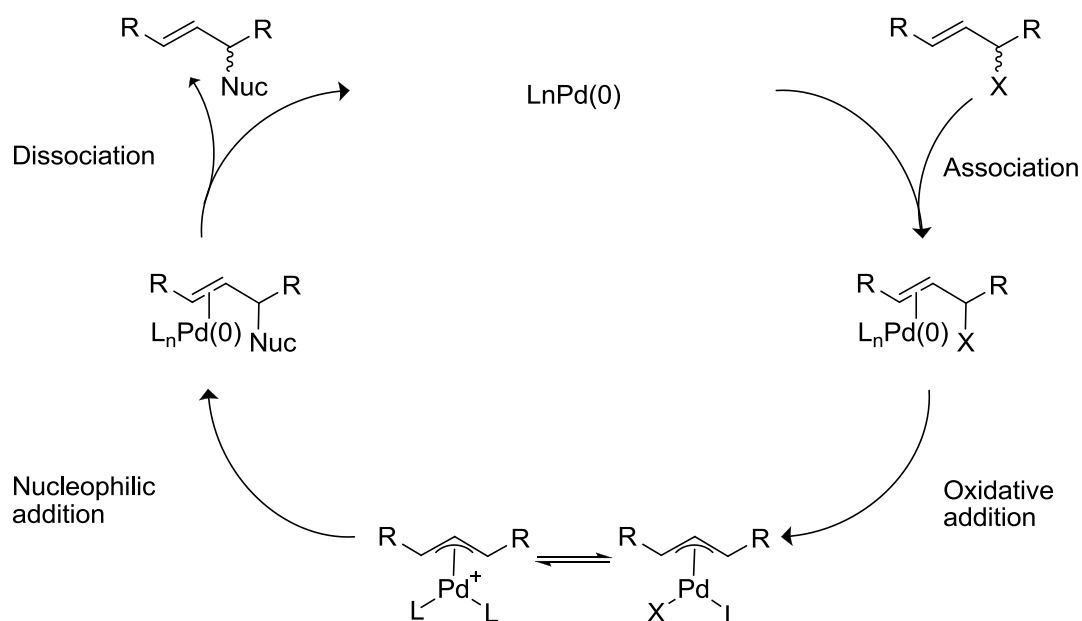


Figure 3.2: Mechanism of palladium catalysed allylic substitution

3.2. Test Reactions

The allyl acetate starting material, the palladium catalyst precursor and the base, *N,O*-bis(trimethylsilyl)acetamide, were synthesised according to literature procedures. The ligand and palladium source were dissolved in dry DCM and stirred together for 30 minutes. The solution was subsequently treated with a solution of 1,3-diphenyl-prop-2-enyl acetate in DCM, followed by dimethyl malonate, *N,O*-bistrimethylsilylacetamide (BSA) and lithium acetate. The base (BSA) generates the nucleophile from dimethyl malonate *in situ*.

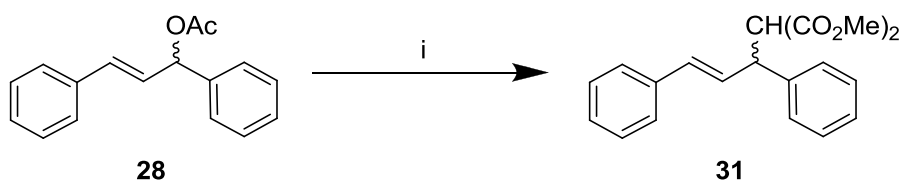


Figure 3.3: Test reaction. i) $[\text{Pd}(\text{C}_3\text{H}_5)_2\text{Cl}]_2$ (2.5 mol%), ligand (10 mol%), $\text{CH}_2(\text{CO}_2\text{Me})_2$, BSA, LiOAc, DCM, RT

The results of our investigation are listed in Table 1. Reactions were performed in duplicate, and consequently yields and ee's are presented as an average of both results (deviation of <3% between runs).

Table 1: Results of catalytic investigations

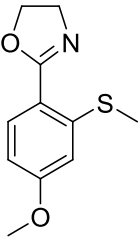
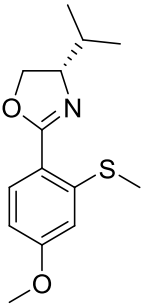
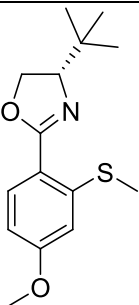
Entry	Ligand	Time (h)	Yield (%) ^a	ee (%) ^b
1	 25	72	77	3 (<i>R</i>)
2	 26	72	86	43 (<i>S</i>)
3	 27	72	92	79 (<i>S</i>)
^a Isolated yields ^b Enantiomeric excess values determined by chiral HPLC. Absolute configuration determined by comparison of sign of optical rotation with literature value				

Table 2 cont.: Results of catalytic investigations

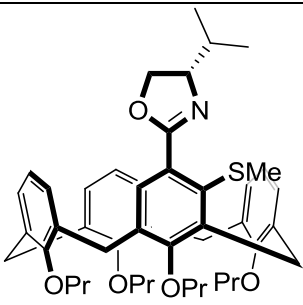
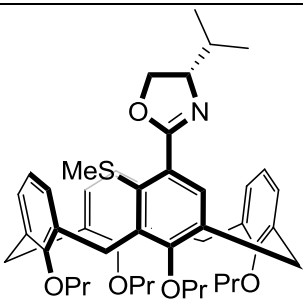
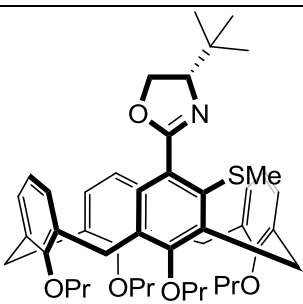
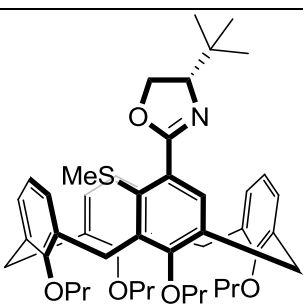
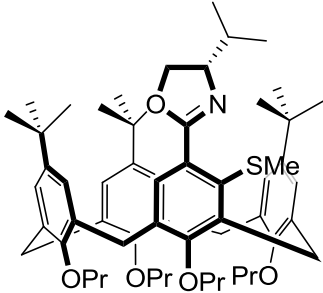
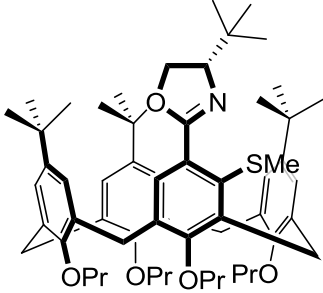
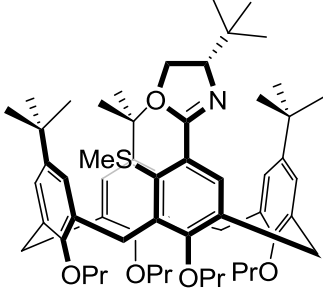
Entry	Ligand	Time (h)	Yield (%) ^a	ee (%) ^b
4	 <p>16-A</p>	24	93	33 (S) (Mismatch)
5	 <p>16-B</p>	24	95	48 (S) (Match)
6	 <p>17-A</p>	24	98	76 (S) (Mismatch)
7	 <p>17-B</p>	24	97	90 (S) (Match)
^a Isolated yields ^b Enantiomeric excess values determined by chiral HPLC. Absolute configuration determined by comparison of sign of optical rotation with literature value				

Table 3 cont.: Results of catalytic investigations

Entry	Ligand	Time (h)	Yield (%) ^a	ee (%) ^b
8	<p>18-A</p> 	1h (decomp)	Trace	n/a
9	<p>19-A</p> 	1h (decomp)	Trace	n/a
10	<p>19-B</p> 	1h (decomp)	Trace	n/a
<p>^a Isolated yields</p> <p>^b Enantiomeric excess values determined by chiral HPLC. Absolute configuration determined by comparison of sign of optical rotation with literature value</p>				

The planar series of ligands, **25-27** (Figure 3.4), was the first to undergo investigation. These ligands displayed good conversion rates of 77-92% yield of the desired allylated product. However, the rate of reaction was undesirably low, with maximum levels of conversion (as recorded in Table 1) reached after 72h. (Extension of reaction time from 72h to 96h showed no appreciable increase in isolated yield). The achiral ligand **25** displayed negligible enantioselectivity, as expected. While we were predicting a value of 0% ee, the 3% ee observed is within the range for statistical deviation. The enantioselectivity displayed increased as steric information was introduced into the ligand system, with isopropyl oxazoline **26** giving 44% ee of the (*S*) enantiomer of **31**. Enantioselectivity was further increased as the steric bulk on the chiral centre increased, with *tert*-butyl oxazoline **27** resulting in an enantiomeric excess of 78%.

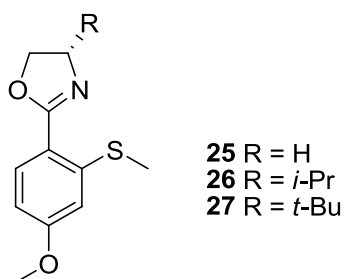


Figure 3.4: Planar ligand series

Following the preliminary test reactions with the planar ligands, attention shifted towards the debutylated calixarene series of ligands, **16-A/B** and **17-A/B** (Figure 3.5). A rate enhancement relative to the planar model compounds was witnessed: complete consumption of the starting material was observed on TLC after 24 hours. The ligands showed good efficiency, as isolated yields were in excess of 90%. With regards to selectivity, it appeared that the effect of the chirality of the carbon adjacent to the oxazoline nitrogen was the foremost stereoselective influence, with all four ligands showing preferential formation of the (*S*) configured product. As was seen for the model compounds, the extent of enantioselectivity increased as the steric bulk on this centre increased, with greater selectivity displayed by the *tert*-butyl oxazolines, **17-A** (77%) and **17-B** (89%), than for the isopropyl oxazolines, **16-A** (31%) and **16-B** (45%). Pleasingly, there was a subtle but significant difference in the selectivity displayed by both diastereomeric pairs. This compares favourably with similar studies using ligands with planar or inherent

chirality. The (*cS*) diastereomers (**16-B** and **17-B**) displayed greater selectivity for the (*S*) configured product than their equivalent (*cR*) diastereomers (**16-A** and **17-B**).

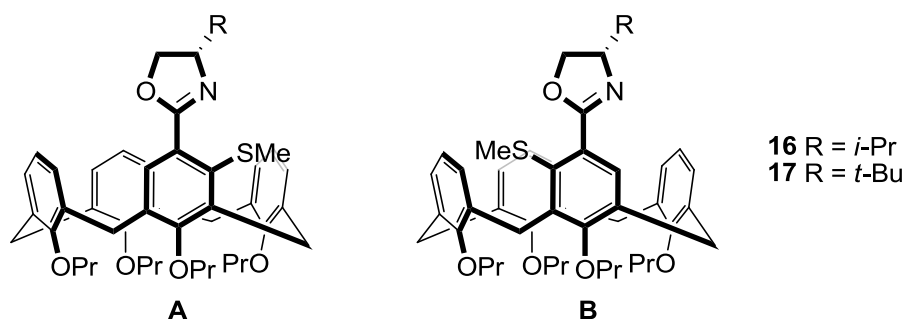


Figure 3.5: Debutylated calixarene series

The next series targeted was the butylated calixarene series, to see if the presence of *tert*-butyl groups on the calixarene bowl had any influence on the stereoselectivity of the reaction. The catalytic investigations of the *tert*-butyl calixarene series (Figure 3.6) were, unfortunately, less successful. The three ligands tested (**18-A**, **19-A**, **19-B**) formed only trace amounts of the allylated product **31**, which could be seen on TLC but could not be isolated. Within 30 minutes of adding the nucleophile to the reaction mixture, palladium black could be seen precipitating out of the solution. ^1H NMR of the reaction mixture revealed that only starting material with no detectable substituted product. If the solution of ligand and palladium source was left to stir without the addition of the nucleophile, decomposition of the complex occurred within a similar timeframe. It is thought that the steric bulk around the co-ordination centre is responsible for the instability of the complex.

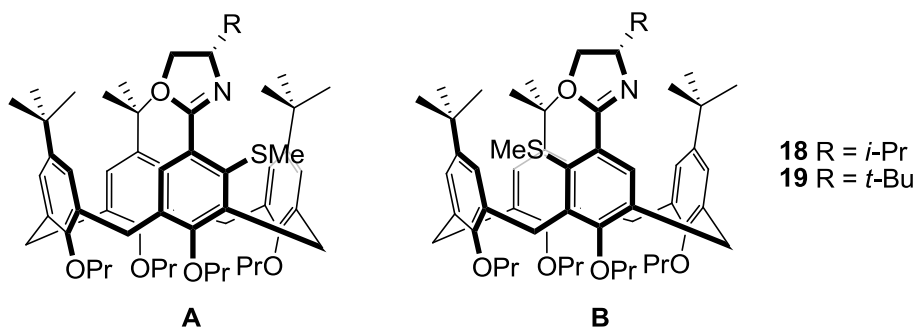


Figure 3.6: Butylated calixarene series

3.3. References

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Chapter 4

Conclusions and Future Work

4.1. Conclusions

The initial aim of this project was to synthesis several inherently chiral calix[4]arenes that could be applied as ligands for asymmetric metal-catalysed reactions. The findings of this project are herewith reported.

The successful synthesis of seven inherently chiral oxazoline thioether calix[4]arenes from *tert*-butylphenol has been reported and discussed. These calixarenes were subsequently employed as ligands in a palladium-catalysed allylic substitution reaction. Three planar model compounds were also synthesised.

The planar series of oxazoline thioether ligands **25-27** (Figure 4.1) showed good conversions (77-92% yield), albeit with a reasonably long time frame (72 h). The enantioselectivity displayed for the achiral ligand **25** was negligible (4% ee, *R*) and increased as steric bulk on the oxazoline chiral centre increased, with *i*-Pr oxazoline **26** giving 44% ee (*S*) and *t*-Bu oxazoline **27** giving 78% ee (*S*).

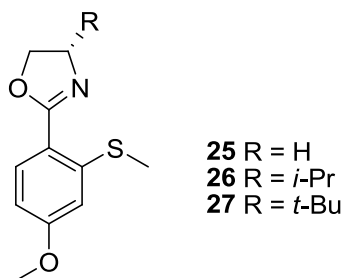


Figure 4.1: Planar model compounds

The use of the debutylated series of oxazoline thioether calixarene ligands (Figure 4.2) achieved high yields (93-98% yield). A rate enhancement relative to a model planar system was also observed, with all catalysed reactions complete within 24 hours. The effect of the central chirality of the chiral oxazoline was found to be the predominant stereoselective influence. Enantioselectivity was greater for the *t*-Bu oxazolines **17-A** (77% ee, *S*) and **17-B** (89% ee, *S*) than

for the *i*-Pr oxazolines **16-A** (31% ee, *S*) and **16-B** (45% ee, *S*). The influence of inherent chirality was investigated and found to play a subtle role, as noticed by others in planar chiral ferrocene work.^{1, 2} The (*cS*) diastereomers **16-B** and **17-B** displayed higher enantioselectivity than their respective (*cR*) diastereomers **16-A** and **17-A**.

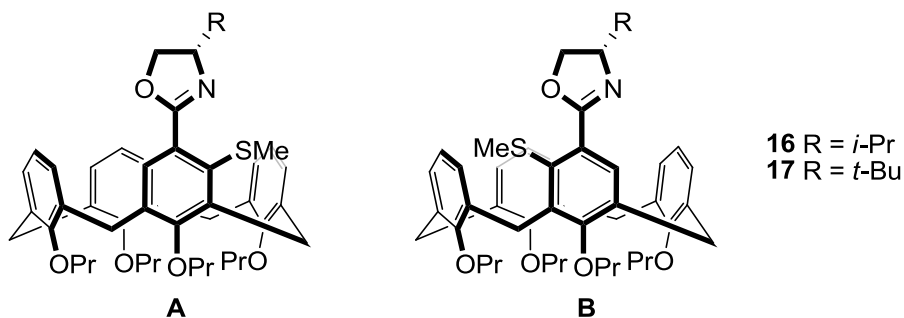


Figure 4.2: Debutylated calixarene series

For the ligands investigated, the (*S*) configured chiral centre on the oxazoline is the predominant stereoselective influence and directs towards the (*S*) configured product. The (*cS*) configured inherent chirality matches this influence, also directing towards the (*S*) configured product, while the (*cR*) configured inherent chirality displays a mismatch, instead directing towards the (*R*) configured product.

Unfortunately, the butylated series of oxazoline thioether calixarenes (Figure 4.3) were unsuccessful as ligands for the palladium catalysed allylic alkylation reaction. These ligands formed unstable complexes that rapidly decomposed, which resulted in palladium black precipitating out of solution and the reaction unable to proceed.

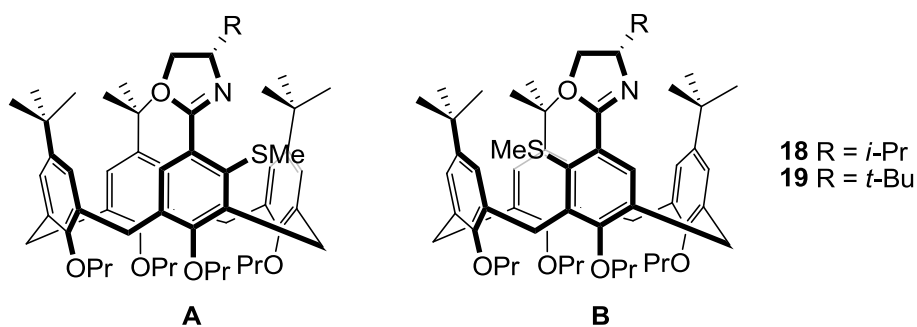


Figure 4.3: Butylated calixarene series

4.2. Future Work

This project represents the first investigation into this class of compounds as ligands for asymmetric catalysis, and consequently presents several avenues for optimisation.

With regards to the use of debutylated oxazoline thioether calixarenes **16-A** to **17-B**, there are several aspects to the catalysis that may be key to optimisation. These include the reaction temperature, solvent, palladium source and palladium : ligand ratio.²⁻⁴

While the catalytic investigations presented in this study were carried out under an atmosphere of argon and in dry solvent, it is possible that trace quantities of oxygen were present, contributing to catalytic inefficiency. Future investigations should include freeze-pump-thaw degassing.

The choice of additive has also been shown to have a significant influence on the outcome of the reaction, with different researchers showing that this needs to be tailored to the ligands used. For example, Dai and co-workers found that, for their ferrocenyl ligands, the choice of salt had subtle effects on the enantioselectivity and yield, but drastic effects on the reaction time, with LiOAc and Cs₂CO₃ having reaction times of 3h and 5h respectively, while KOAc and NaOAc gave reaction times of 48h each.¹ Conversely, Mi and coworkers found that the choice of salt additive had significant effects on the enantioselectivity in palladium catalysed allylic alkylation.³ Consequently, a variety of additives should be tested to investigate the effect that they have on reaction outcomes.

Increasing the steric bulk on the thioether should also have an effect on the stereoselectivity in catalysis. The use of alternate electrophile sources to quench after ortholithiation will allow facile

synthesis of a larger library of thioethers. In particular, phenylthioether-oxazoline compounds have been successfully employed as asymmetric ligands on numerous occasions.^{1, 2, 5}

4.3. References

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Chapter 5

Experimental

5.1. General Procedures

All chemicals used in this investigation were purchased from Aldrich or Merck. Diethyl ether, tetrahydrofuran, pentane and toluene were distilled under nitrogen from sodium sand with benzophenone as an indicator. Dichloromethane was distilled under nitrogen from calcium hydride. Where necessary, purification of other reagents was performed according to standard literature procedures.¹ The molarity of alkyl lithiums was determined using a method as described in the literature.²

All reactions were performed under anhydrous conditions and a positive pressure of argon or nitrogen, unless otherwise stated. Standard Schlenk techniques were employed where necessary. Low temperature reactions were performed in a Dewar using dry ice in acetone (−78 °C) or ice in water (0 °C). Reactions require extended low temperature control were performed in a Dewar that was regulated with a Thermo Scientific Haake EK90 Immersion Cooler. High vacuum refers to pressure less than 1 mmHg.

All chromatography was performed using combinations of petroleum ether (PET), ethyl acetate (EtOAc), dichloromethane (DCM), chloroform (CHCl₃) and/or toluene (PhMe) as solvent. Thin layer chromatography (TLC) was carried out on aluminium backed Merck silica gel 60 F₂₅₄ plates. Visualisation was achieved with a UV lamp, using iodine on silica or by spraying with a Cerium Ammonium Molybdate solution (CAM) or ninhydrin solution (NIN) followed by heating. Column chromatography was performed on Merck silica gel 60 (particle size 0.040-0.063 mm).

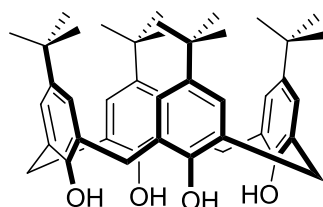
All ¹H and ¹³C nuclear magnetic resonance spectra were obtained using a 300 MHz Varian VNMRS (75 MHz for ¹³C) or 400 MHz Variety Unity Inova (100 MHz for ¹³C) using deuterated chloroform as solvent. Chemical shifts (δ) were recorded using the residual chloroform peaks (δ 7.26 in ¹H NMR and δ 77.0 in ¹³C NMR). All chemical shifts are reported in ppm. Spectra were obtained at 25 °C, unless otherwise stated.

Melting points were obtained using a Gallenkamp Melting Point Apparatus and are uncorrected. Infrared spectra were obtained using a Nexus Thermo-Nicolet FT-IR instrument using thin film solutions of dichloromethane on NaCl plates, or using the ATR attachment. High resolution mass spectrometry was performed by the CAF (Central Analytical Facility) Institute at Stellenbosch University using a Waters API Q-TOF Ultima spectrometer.

5.2. Compounds

5.2.1. Calixarenes

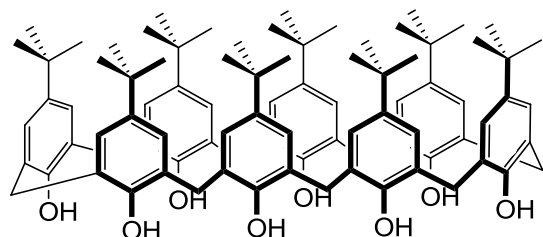
5,11,17,23-tetra-*tert*-butyl-calix[4]arene **1**³⁻⁵



p-*tert*-Butylphenol (83.2 g, 553.9 mmol) was placed in a dry 2L 3-necked flask. The flask was placed in a heating mantel and fitted with an overhead mechanical stirrer. Formaldehyde (51.6 ml, 37% in aqueous solution) was added to the flask, followed by sodium hydroxide (0.467 g in 3 ml H₂O). The flask was subsequently fitted with a nitrogen inlet, and an outlet which passed through a beaker of water. A steady flow of nitrogen was maintained. The reaction mixture was rapidly heated to 130 °C for approximately 30 min, until a pale yellow-green solid was formed. Heating was immediately stopped and diphenyl ether (560 ml) was added. The heterogeneous mixture was stirred overnight. Thereafter, toluene (40 ml) was added and the solution heated to 180 °C to drive off H₂O as an azeotrope. The outlet was fitted with a reflux condenser (cooling with compressed air) and the solution heated to reflux (approximately 260 °C) for 4h. The honey-coloured solution was allowed to cool before EtOAc (480 ml) was added. The solution was stirred for a further hour. The product was then isolated by filtration. The cream-coloured solid was triturated with acetic acid (40 ml), then filtered and washed with EtOAc (4 x 20 ml) and finally dried under high vacuum to yield **1** as a fine white powder (66.50g, 102.5 mmol, 74%). Further purification could be achieved by recrystallization from boiling toluene to afford a calixarene-toluene co-crystal. Characterisation data conformed to literature data.³⁻⁵

Mp 338 °C; R_f = 0.58 (50% DCM in PET); IR (ATR, cm^{-1}): 3154 (s, OH), 2960 (s, CH), 1500 (C=C), 1200 (s, C-O); ^1H NMR (300 MHz, CDCl_3) δ ppm 1.22 (s, 36 H, $\text{C}(\text{CH}_3)_3$), 3.44 - 3.58 (m, 4H, ArCH_2Ar), 4.18 - 4.36 (m, 4H, ArCH_2Ar), 7.06 (s, 8H, ArH), 10.35 (s, 4H, ArOH); MS (ESI+): m/z (%) = 648 (100) $[\text{M}]^+$; HRMS–Positive: m/z $[\text{M}]^+$ calcd for $\text{C}_{44}\text{H}_{54}\text{O}_4$: 648.9712; found: 648.4091.

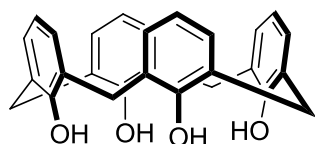
5,11,17,23,29,35,41,47-octa-tert-butyl-49,50,51,52,53,54,55,56-octahydroxycalix[8]arene [1A]⁵



Calix[8]arene **1A** was synthesised in a procedure analogous to that for **1** from *p*-*t*-butylphenol (81.2 g, 541 mmol); however, after driving off the water-toluene azeotrope, the solution was stirred at 180 °C for 4 hours (instead of heating to 260 °C). Purification yielded **1A** as a white powder (51.5 g, 40.0 mmol, 59%). Characterisation data conformed to literature data.⁵

Mp 407-410 °C; IR (ATR, cm^{-1}): 3207 (s, H), 2960 (s, CH), 1500 (C=C), 1202 (S, C-O); ^1H NMR (300 MHz, CDCl_3) δ ppm 1.27 (s, 72H, $\text{C}(\text{CH}_3)_3$), 3.51 (d, J = 13.1 Hz, 8H, $\text{ArCH}_{\text{eq}}\text{HAr}$), 4.38 (d, J = 13.1 Hz, 8H, $\text{ArCH}_{\text{ax}}\text{HAr}$), 7.19 (s, 16H, ArH), 9.63 (s, 8H, OH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 31.63 (ArCH_2Ar), 32.48 ($\text{C}(\text{CH}_3)_3$), 34.17 ($\text{C}(\text{CH}_3)_3$), 125.66 (C_{ArH}), 129.88 (C_{ArCH_2}), 148.33 (C_{ArOH}); MS (ESI+): m/z (%) = 1295 (100) $[\text{M}]^+$; HRMS–Positive: m/z $[\text{M}]^+$ calcd for $\text{C}_{88}\text{H}_{111}\text{O}_8$: 1295.8279; found: 1295.8301.

25,26,27,28-tetrahydroxycalix[4]arene [2]⁶

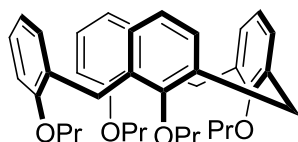


t-Butylcalixarene **1** (5.0 g, 7.71 mmol) was placed in an oven-dried 250 ml 3-necked round-bottomed flask under a positive pressure of argon. Phenol (0.875 g, 9.31 mmol, 1.2 eq) and dry toluene (35 ml) were added and the solution stirred for 10 minutes. With vigorous stirring, aluminium trichloride (5.13 g, 38.55 mmol, 5 eq) was rapidly added and the reaction mixture stirred for 2 hours. The

reaction mixture was poured into a beaker with ice (100 g), taking care as HCl(g) was rapidly evolved. The reaction vessel was washed with small portions of dichloromethane and crushed ice to quantitatively transfer all of the viscous material. Once the ice had melted the solution was extracted into DCM (2 x 150 ml). The combined extracts were washed with concentrated HCl (2 x 150 ml), brine (150 ml) and H_2O (150 ml). The organic layer was dried over MgSO_4 and the solvent removed under reduced pressure. The residue was triturated with diethyl ether (100 ml) to yield the product **2** as a fine white powder (2.16 g, 5.17 mmol, 67%). Further purification could be achieved by recrystallization from dichloromethane and methanol. Characterisation data conformed to literature data.⁶

Mp 310-313 °C (DCM/MeOH); R_f = 0.21 (25% DCM in PET); IR (ATR, cm^{-1}): 3144 (s, OH), 1195 (s, C-O); ^1H NMR (300 MHz, CDCl_3) δ ppm 3.58 (s, 4H, ArCH_2Ar), 4.28 (s, 4H, ArCH_2Ar), 6.75 (t, J = 7.5 Hz, 4H, ArH), 7.06 (d, J = 7.5 Hz, 8H, ArH), 10.22 (s, 4H, ArOH). ^{13}C NMR (75 MHz, CDCl_3) δ ppm 31.70 (ArCH_2Ar), 122.23 (C_{ArH}), 128.22 (C_{ArH}), 128.96 (C_{ArCH_2}), 148.76 (C_{ArOH}).

25,26,27,28-tetrapropoxycalix[4]arene [**3**]⁷

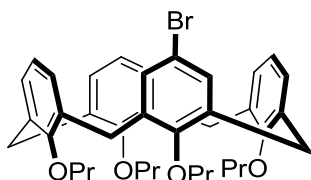


Sodium hydride (1.461 g, 60% dispersion in mineral oil) was added to a dry 100 ml 3-necked flask under a positive pressure of argon and washed with petroleum ether (3 x 5 ml). Dry dimethyl formamide (30 ml) was added cautiously. Calixarene **2** (1.46 g, 3.44 mmol) was added to this solution, followed by 1-iodopropane (3.4 ml, 34.8 mmol, 10 eq). The reaction was stirred at room temperature for 14 hours before being carefully quenched with 2M HCl (60 ml). The precipitate was filtered and washed with H_2O (60 ml), then transferred to a 50 ml Erlenmeyer flask. Methanol (10 ml) was added to the flask and the mixture gently heated to 60 °C. Once all the material had dissolved, the flask was placed in the refrigerator for 3 hours. The product **3** was collected by filtration to yield white crystals (1.58 g, 2.59 mmol, 75%). Characterisation data conformed to literature data.⁷

Mp 249-251 °C (MeOH); R_f = 0.25 (35% DCM in PET); IR (ATR, cm^{-1}): 2960 (s, CH), 1500 (C=C), 1244 (s, C-O); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.02 (t, J = 7.4 Hz, 12H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.91 - 2.00 (m, 8H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 3.16 (d, J = 13.4 Hz, 4H, $\text{ArCH}_{\text{eq}}\text{HAr}$), 3.86 (t, J = 7.4 Hz, 8H, $\text{OCH}_2\text{CH}_2\text{CH}_3$), 4.47 (d, J =

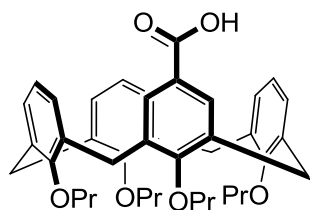
13.4 Hz, 4H, $\text{ArCH}_{\text{ax}}\text{HAr}$), 6.57 - 6.65 (m, 12H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 10.32 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 23.24 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 30.97 (ArCH_2Ar), 76.66 (OCH_2CH_2) 121.83 ($\text{C}_{\text{Ar}}\text{H}$), 128.08 ($\text{C}_{\text{Ar}}\text{H}$), 136.11 ($\text{C}_{\text{Ar}}\text{CH}_2$), 156.58 ($\text{C}_{\text{Ar}}\text{OH}$).

5-bromo-25,26,27,28-tetrapropoxycalix[4]arene **4**⁸



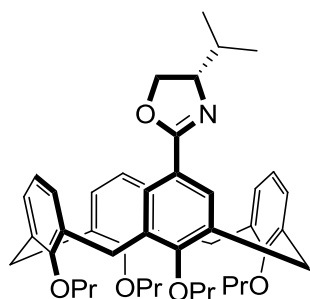
To a solution of calix[4]arene **3** (1.4 g, 2.36 mmol) in freshly distilled 2-butanone (25 ml) was added *N*-bromosuccinimide (420 ml, 2.36 mmol, 1.0 eq). The reaction mixture was stirred in a foil-wrapped flask at room temperature for 24 hours. The solvent was removed under reduced pressure and the residue dissolved in 10% chloroform in petroleum ether. Any excess NBS that precipitated out was filtered off. The solvent was once again removed to produce bromo calixarene **4** as a white solid (1.45 g, 2.16 mmol, 91%). Further purification could be achieved by recrystallization from 10% dichloromethane in ethanol. Characterisation data conformed to literature data.⁸

Mp 157 °C (DCM/EtOH); R_f = 0.40 (5% CHCl_3 in PET); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.93 (t, J = 7.5 Hz, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.05 - 1.12 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.84 - 1.97 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.12 - 3.22 (m, 4H, ArCH_2Ar), 3.71 - 3.87 (m, 4H, OCH_2CH_2), 3.87 - 4.04 (m, 4H, OCH_2CH_2), 4.45 (dd, J = 13.7, 3.1 Hz, 4H, ArCH_2Ar), 6.28 (d, J = 7.6 Hz, 2H, ArH), 6.51 - 6.57 (m, 3H, ArH), 6.83 - 6.96 (m, 4H, ArH), 7.00 (dd, J = 7.3, 1.3 Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 9.92, 10.53, 10.65, 23.02, 23.35, 23.41, 30.73, 30.95, 76.68, 76.75, 105.44, 119.73, 122.16, 122.24, 127.61, 128.42, 129.40, 131.65, 133.73, 135.15, 135.89, 136.76, 155.56, 157.32, 159.52.

5-carboxy-25,26,27,28-tetrapropoxycalix[4]arene [5]⁹

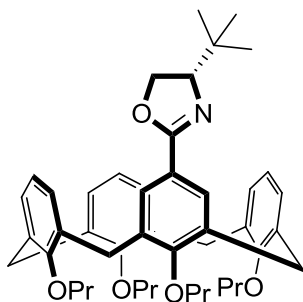
Bromo calixarene **4** (360 mg, 0.54 mmol) was weighed out in an oven-dried Schlenk flask and dried under high vacuum overnight. The calixarene was dissolved in dry THF (5 ml), the solvent removed under reduced pressure and the flask placed under high vacuum for 1 hour. This process was performed a total of three times. Thereafter, dry THF (20 ml) and sodium hydride (60% NaH in mineral oil, 100 mg) were added to the flask and the solution stirred at room temperature for 1 hour. The flask was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-BuLi (0.7 ml, 0.86 mmol, 1.6 eq) was added dropwise under a constant pressure of argon. The mixture was stirred for a further hour before being rapidly poured onto freshly condensed powdered CO_2 (400 ml). The beaker was allowed to warm to room temperature. The residue was dissolved in EtOAc (150 ml) and washed with successive portions of 1M HCl (50 ml), H_2O (100 ml) and saturated NaHCO_3 (50 ml). The organic layer was dried over MgSO_4 before the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (gradient elution: 10% EtOAc in PET to 50% EtOAc in PET), resulting in carboxylic acid **5** as a white solid (273 mg, 0.43 mmol, 80%). Characterisation data conformed to literature data.⁹

Mp $275\text{--}278\text{ }^{\circ}\text{C}$ (MeOH); $R_f = 0.65$ (40% EtOAc in PET); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.96 - 1.07 (m, 12 H, CH_2CH_3), 1.85 - 1.99 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.17 (d, $J = 13.7\text{ Hz}$, 2H, ArCH_2Ar), 3.80 - 3.91 (m, 6H, OCH_2CH_2), 3.94 (t, $J = 7.3\text{ Hz}$, 2H, OCH_2CH_2), 4.41 - 4.50 (m, 4H, ArCH_2Ar), 6.48 - 6.58 (m, 3H, ArH), 6.60 - 6.69 (m, 6H, ArH), 7.33 (s, 2H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 10.27, 10.31, 10.35, 23.21, 23.25, 23.32, 30.95, 76.60, 76.68, 76.74, 121.86, 122.16, 122.63, 128.11, 128.20, 128.56, 130.43, 134.45, 134.95, 135.36, 135.53, 156.43, 156.54, 161.63, 172.09.

5-((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-25,26,27,28-tetrapropoxycalix[4]arene [6]⁹

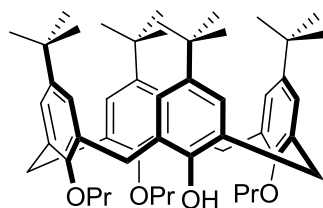
Carboxylic acid **5** was placed in an oven-dried 100 ml round-bottomed flask, together with dry DCM (20 ml) and oxalyl chloride (0.45 ml, 5.1 mmol, 4.9 eq). The flask was stirred at room temperature for 24 hours. The solvent was subsequently removed under reduced pressure, while maintaining inert conditions, and the residual foam was dried under high vacuum for 2 hours. The acid chloride was then dissolved in dry DCM (15 ml) and added to a mixture of L-valinol (120 mg, 1.19 mmol, 1.14 eq), Et₃N (0.35 ml, 2.55 mmol, 2.45 eq) and dry DCM (15 ml) at 0 °C, using a syringe pump to achieve an addition rate of 30 ml per hour. The solution was warmed to room temperature and stirred for 24 hours. The solvent was subsequently removed under reduced pressure and the amide intermediate purified by silica gel column chromatography (gradient elution: 20% EtOAc in PET to 50% EtOAc in PET). The white solid product was dissolved in dry DCM (20 ml) and to this solution were added Et₃N (0.75 ml, 5.4 mmol, 5.5 eq) and mesyl chloride (0.2 ml, 2.6 mmol, 2.7 eq). This solution was stirred at room temperature for 24 hours. DCM (50 ml) and saturated NaHCO₃ were added. The layers were separated and the aqueous phase extracted with a further portion of DCM (50 ml). The combined organics were washed with 2M NaOH (30 ml), dried over MgSO₄ and the solvent removed under reduced pressure. Purification of the solid residue was achieved by silica gel column chromatography (6% EtOAc in PET), yielding **6** as a white solid (640 mg, 0.90 mmol, 87%). Characterisation data conformed to literature data.⁹

Mp 115-120 °C; [α]_D¹⁸ = -14.3° (c 0.27, DCM); R_f = 0.55 (10% EtOAc in PET); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.92 - 0.98 (m, 9H, CH₂CH₃, CH(CH₃)₂), 1.83 - 2.00 (m, 9H, CH₂CH₂CH₃), 3.16 (d, *J* = 13.5 Hz, 2H, ArCH₂Ar), 3.21 (d, *J* = 13.5 Hz, 1H, ArCH₂Ar), 3.22 (d, *J* = 13.5 Hz, 1H, ArCH₂Ar), 3.76 (t, *J* = 7.1 Hz, 4H, OCH₂CH₃), 3.90 - 4.03 (m, 4H, OCH₂CH₂), 4.04 - 4.15 (m, 1H, OCH₂CHN), 4.31 - 4.41 (m, 2H, OCH₂CHN), 4.45 (d, *J* = 13.5 Hz, 4H, ArCH₂Ar), 6.33 - 6.42 (m, 6H, ArH), 6.71 (t, *J* = 7.4 Hz, 1H, ArH), 6.85 (d, *J* = 7.4 Hz, 2H, ArH), 7.47 (d, *J* = 2.2 Hz, 1H, ArH), 7.52 (d, *J* = 2.2 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ ppm 10.06, 10.56, 17.95, 19.14, 23.09, 23.12, 23.37, 30.87, 30.96, 32.81, 69.74, 72.47, 76.51, 76.60, 76.80, 76.83, 121.22, 121.78, 122.05, 127.83, 127.87, 128.47, 128.53, 128.62, 133.52, 134.12, 136.12, 136.15, 136.24, 155.75, 157.28, 160.27, 163.62.

5-((S)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-25,26,27,28-tetrapropoxycalix[4]arene [7]¹⁴

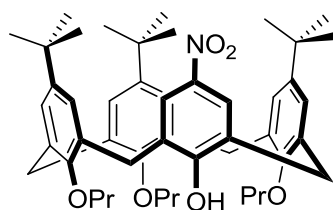
Carboxylic acid **5** (230 mg, 0.36 mmol), oxalyl chloride (0.1 ml, 1.1 mmol, 3 eq) and dry DCM (3 ml) were added to an oven-dried round-bottomed flask. After stirring at room temperature for 3 hours, the solvent was removed under reduced pressure. The solid residue was dissolved in dry DCM (3 ml) and added dropwise to a stirring solution of L- *tert*-leucinol (50 mg, 0.43 mmol, 1.2 eq), Et₃N (0.3 ml, 2.2 mmol, 6 eq) in DCM (3 ml) at 0 °C. The solution was allowed to stir overnight while warming to room temperature. Mesyl chloride (0.1 ml, 1.1 mmol, 3 eq) was subsequently added to the flask and the mixture stirred for an additional 3 hours. Thereafter, H₂O (5 ml) and DCM (20 ml) were added, the layers separated and the aqueous phase extracted with DCM (15 ml). The organic layers were combined and dried over MgSO₄. The solvent was removed under reduced pressure and the solid residue purified through the use of silica gel column chromatography (5% EtOAc in PET), yielding **7** as a white translucent solid (206 mg, 0.26 mmol, 80%). Characterisation data conformed to literature data.¹⁴

Mp 145-146 °C (DCM); $[\alpha]_D^{19} = -16.3^\circ$ (c 2.2, DCM); $R_f = 0.53$ (10% EtOAc in PET); ¹H NMR (300 MHz, CDCl₃) δ ppm 0.90 - 0.99 (m, 15H, C(CH₃)₃, CH₂CH₃), 1.06 (t, $J = 7.4$ Hz, 6H, CH₂CH₃), 1.82 - 2.03 (m, 8H, CH₂CH₂CH₃), 3.12 - 3.26 (m, 4H, ArCH₂Ar), 3.76 (t, $J = 7.0$ Hz, 4H, OCH₂CH₂), 3.91 - 4.07 (m, 5H, OCH₂CH₂, OCH₂CHN), 4.21 (dd, $J = 8.6, 7.7$ Hz, 1H, OCH₂CHN), 4.32 (dd, $J = 10, 8.6$ Hz, 1H, OCH₂CHN), 4.46 (d, $J = 13.4$ Hz, 4H, ArCH₂Ar), 6.31 - 6.43 (m, 6H, ArH), 6.72 (m, 1H, ArH), 6.84 - 6.89 (m, 2H, ArH), 7.48 (d, $J = 2.2$ Hz, 1H, ArH), 7.54 (d, $J = 2.2$ Hz, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ ppm 10.03, 10.57, 23.08, 23.10, 23.36, 25.92, 30.84, 30.87, 30.90, 30.95, 34.03, 68.47, 76.09, 76.50, 76.58, 76.78, 76.81, 121.26, 121.76, 122.01, 127.75, 127.85, 128.45, 128.55, 128.66, 133.45, 133.49, 134.05, 134.07, 136.12, 136.17, 136.20, 155.71, 157.30, 160.24, 163.53.

5,11,17,23-tetra-*tert*-butyl-26,27,28-tripropoxycalix[4]arene [8]¹⁰

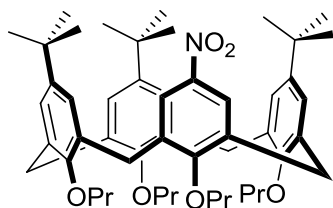
t-Butylcalixarene **1** (12.2 g, 16.3 mmol), barium oxide (17.6 g, 94.5 mmol, 5.8 eq), barium hydroxide octahydrate (20.8 g, 54 mmol, 3.3 eq) and freshly distilled dimethyl formamide (240 ml) were added to a dry 500 ml round-bottomed flask. The mixture was stirred at room temperature under argon for 15 minutes. Propyl iodide (55 ml, 459 mmol, 28 eq) was slowly added and the solution stirred for a further 2h. The reaction mixture was then poured into 1M HCl (200 ml) and extracted with ethyl acetate (2 x 250 ml). The organic layers were combined and washed with H₂O (3 x 100 ml), followed by drying over MgSO₄. The solvent was removed by rotary evaporation. Purification was achieved by crystallization from DCM (20 ml) and ethanol (60 ml) affording **8** as pale yellow crystals (10.2 g, 13.2 mmol, 81%). Characterisation data conformed to literature data.¹⁰

Mp 188-190 °C (EtOH/DCM); *R*_f = 0.65 (50% DCM in PET); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.83 (s, 18H, C(CH₃)₃), 0.96 (t, *J* = 7.5 Hz, 3H, CH₂CH₃), 1.10 (t, *J* = 7.5 Hz, 6H, CH₂CH₃), 1.33 (s, 9H, C(CH₃)₃), 1.81 - 2.03 (m, 4H, CH₂CH₂CH₃), 2.27 - 2.41 (m, 2H, CH₂CH₂CH₃), 3.17 (d, *J* = 12.6 Hz, 2H, ArCH₂Ar), 3.24 (d, *J* = 13.1 Hz, 2H, ArCH₂Ar), 3.73 - 3.79 (m, 4H, OCH₂CH₂), 3.82 - 3.89 (m, 2H, OCH₂CH₂), 4.34 (d, *J* = 13.1 Hz, 2H, ArCH₂Ar), 4.38 (d, *J* = 12.6 Hz, 2H, ArCH₂Ar), 5.58 (s, 1H, ArOH), 6.50-6.55 (m, 4H, ArH), 7.06 (s, 2H, ArH), 7.14 (s, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ ppm, 9.62 (CH₂CH₃), 10.79 (2 x CH₂CH₃), 22.45 (CH₂CH₂CH₃), 23.40 (2 x CH₂CH₂CH₃), 31.06 (2 x C(CH₃)₃), 31.09 (ArCH₂Ar), 31.09 (ArCH₂Ar), 31.36 (C(CH₃)₃), 31.69 (C(CH₃)₃), 31.76 (C(CH₃)₃), 33.63 (2 x C(CH₃)₃), 34.11 (C(CH₃)₃), 76.28 (OCH₂CH₂), 77.81 (2 x OCH₂CH₂), 124.65 (C_{Ar}H), 124.75 (C_{Ar}H), 124.96 (C_{Ar}H), 125.57 (C_{Ar}H), 129.50 (C_{Ar}CH₂), 131.83 (C_{Ar}CH₂), 136.01 (C_{Ar}CH₂), 141.40 (CC(CH₃)₃), 144.97 (2 x CC(CH₃)₃), 145.48 (CC(CH₃)₃), 150.67 (2 x C_{Ar}OCH₂), 153.94 (C_{Ar}OH).

11,17,23-tri-*tert*-butyl-5-nitro-26,27,28-tripropoxycalix[4]arene [9]¹¹

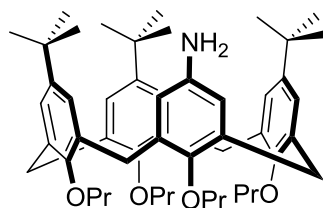
Tripropoxy calixarene **8** (4.5 g, 5.8 mmol), dichloromethane (50 ml) and acetic acid (29 ml) were added to a 250 ml round-bottomed flask. The solution was cooled to 0 °C and stirred for 10 minutes. Thereafter, 65% nitric acid (2.9 ml, 42 mmol, 7.2 eq) was added dropwise. The solution was allowed to warm to room temperature, and the progress of the reaction closely followed via TLC. The reaction was quenched after approximately 10 minutes with the addition of H₂O (50 ml). The organic and aqueous phases were separated. The aqueous portion was extracted with dichloromethane (50 ml). The organic layers were combined and washed successively with H₂O (2 x 50 ml), saturated NaHCO₃ solution (2 x 50 ml) and an additional portion of H₂O (50 ml). The organic extract was dried over MgSO₄ before the solvent was removed under reduced pressure. The residue was purified by slow crystallisation from dichloromethane (20 ml) and ethanol (50 ml), yielding **9** as light yellow crystals (3.45 g, 4.43 mmol, 76%). Characterisation data conformed to literature data.¹¹

Mp 180 °C (EtOH/DCM); *R_f* = 0.33 (3% EtOAc in PET); ¹H NMR (300 MHz, CDCl₃) δ ppm 0.84 (s, 18H, C(CH₃)₃), 0.97 (t, *J* = 7.5 Hz, 3H, CH₂CH₃), 1.11 (t, *J* = 7.5 Hz, 6H, CH₂CH₃), 1.36 (s, 9H, C(CH₃)₃), 1.81-2.05 (m, 4H, CH₂CH₂CH₃), 2.21-2.35 (m, 2H, CH₂CH₂CH₃), 3.22 (d, *J* = 13.5 Hz, 2H, ArCH₂Ar), 3.41 (d, *J* = 13.5 Hz, 2H, ArCH₂Ar), 3.70-3.88 (m, 6H, OCH₂CH₂), 4.29 – 4.39 (m, 4H, ArCH₂Ar), 6.46 (d, *J* = 2.5 Hz, 2H, ArH), 6.63 (d, *J* = 2.5 Hz, 2H, OCH₂CH₂), 7.17 (s, 2H, ArH), 7.24 (s, 1H, C_{Ar}OH), 8.07 (s, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ ppm 9.55 (CH₂CH₃), 10.72 (2 x CH₂CH₃), 22.56 (CH₂CH₂CH₃), 23.34 (2 x CH₂CH₂CH₃), 31.05 (ArCH₂Ar), 31.07 (C(CH₃)₃), 31.30 (ArCH₂Ar), 31.66 (C(CH₃)₃), 33.76 (2 x C(CH₃)₃), 34.18 (C(CH₃)₃), 76.12 (OCH₂CH₂), 78.01 (2 x OCH₂CH₂), 124.26 (C_{Ar}H), 124.37 (C_{Ar}H), 125.66 (C_{Ar}H), 125.68 (C_{Ar}H), 129.76 (C_{Ar}CH₂), 129.78 (C_{Ar}CH₂), 132.62 (C_{Ar}CH₂), 135.77 (C_{Ar}CH₂), 139.25 (C_{Ar}NO₂), 145.79 (2 x CC(CH₃)₃), 145.82 (CC(CH₃)₃), 151.68 (2 x C_{Ar}OCH₂), 153.75 (C_{Ar}OCH₂), 159.98 (C_{Ar}OH)

11,17,23-tri-*tert*-butyl-5-nitro-25,26,27,28-tetrapropoxycalix[4]arene [10]

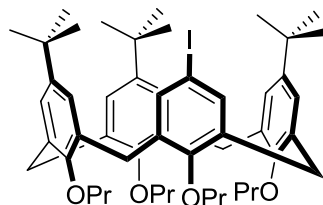
Nitro calixarene **9** (6.4 g, 8.4 mmol), sodium carbonate (1.8 g, 17 mmol, 2 eq) and acetonitrile (65 ml) were added to a dry 150 ml round-bottomed flask. The solution was brought to reflux under argon. After 30 minutes at reflux, 1-iodopropane (15 ml, 154 mmol, 18.3 eq) was added. The reaction was held at reflux for 48 hours. Thereafter, it was cooled to room temperature and the contents of the flask added to H₂O (100 ml) and ethyl acetate (250 ml). The layers were separated and the aqueous fraction extracted with an additional portion of ethyl acetate (50 ml). The organic fractions were combined and washed with 1M HCl (100 ml) and brine (50 ml). After drying over MgSO₄, the solvent was removed under reduced pressure. Purification was achieved by slow crystallisation from dichloromethane (20 ml) and ethanol (60 ml) affording white crystals of **10** (6.11 g, 7.56 mmol, 90%). Characterisation data conformed to literature data.¹⁴

Mp 218 °C (EtOH/DCM); *R*_f = 0.55 (7% EtOAc in PET); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.65 (s, 9H, C(CH₃)₃), 0.94 (t, *J* = 7.5 Hz, 6H, CH₂CH₃), 1.08 - 1.14 (m, 6H, CH₂CH₃), 1.39 (s, 18H, C(CH₃)₃), 1.85 - 1.97 (m, 4H, CH₂CH₂CH₃), 1.97 - 2.13 (m, 4H, CH₂CH₂CH₃), 3.12 - 3.21 (m, 4H, ArCH₂Ar), 3.69 (t, *J* = 6.8 Hz, 2H, OCH₂CH₂), 3.74 (t, *J* = 6.8 Hz, 2H, OCH₂CH₂), 3.91 - 3.98 (m, 2H, OCH₂CH₂), 4.03 - 4.11 (m, 2H, OCH₂CH₂), 4.43 (d, *J* = 13.0 Hz, 2H, ArCH₂Ar), 4.48 (d, *J* = 13.0 Hz, 2H, ArCH₂Ar), 6.23 (s, 2H, ArH), 7.14 (d, *J* = 2.5 Hz, 2H, ArH), 7.17 (d, *J* = 2.5 Hz, 2H, ArH), 7.28 (s, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ ppm 9.82, 10.62, 10.84, 23.05, 23.40, 23.57, 30.68, 31.06, 31.14, 31.68, 33.12, 34.15, 76.52, 77.13, 77.67, 123.07, 124.43, 125.13, 126.66, 131.86, 134.16, 135.15, 136.23, 142.52, 144.37, 145.34, 152.64, 154.72, 160.65.

11,17,23-tri-*tert*-butyl-5-amino-25,26,27,28-tetrapropoxycalix[4]arene [11]¹²

Nitro calixarene **10** (6.12 g, 7.6 mmol) was dissolved in ethanol (80 ml). To this solution was added 10% palladium on carbon (0.8 g, 0.76 mmol, 0.1 eq). The mixture was heated to reflux. Hydrazine hydrate (1 ml, 20 mmol, 2.6 eq) was slowly added and the solution stirred at reflux for 2 hours. Thereafter, the flask was cooled to room temperature and its contents filtered through Celite. The Celite was washed with dichloromethane (30 ml). Rapid formation of small white crystals occurred in the standing filtrate, giving a **DCM·11** solvate (5.5 g, 6.95 mmol, 92%). The DCM could be removed by heating the crystals under vacuum. Characterisation data conformed to literature data.¹²

Mp 190-191 °C (EtOH/DCM); R_f = 0.46 (5% EtOAc in PET); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.80 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.92 (t, J = 7.5 Hz, 6H, CH_2CH_3), 1.04 - 1.13 (m, 6H, CH_2CH_3), 1.35 (s, 18H, $\text{C}(\text{CH}_3)_3$), 1.83 - 1.97 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.00 - 2.11 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.02 (d, J = 12.7 Hz, 2H, ArCH_2Ar), 3.13 (d, J = 12.9 Hz, 2H, ArCH_2Ar), 3.60 (t, J = 7.0 Hz, 2H, OCH_2CH_2), 3.72 (t, J = 7.0 Hz, 2H, OCH_2CH_3), 3.92 - 4.03 (m, 4H, OCH_2CH_2), 4.38 (d, J = 12.7 Hz, 2H, ArCH_2Ar), 4.46 (d, J = 12.9 Hz, 2H, ArCH_2Ar), 5.71 (s, 2H, ArH), 6.29 (s, 2H, ArH), 7.02 (d, J = 2.5 Hz, 2H, ArH), 7.10 (d, J = 2.5 Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 9.86, 10.76, 10.82, 23.02, 23.40, 23.56, 30.97, 31.09, 31.20, 31.73, 33.46, 34.03, 76.49, 77.04, 77.31, 114.76, 124.48, 125.21, 125.70, 132.27, 133.86, 135.33, 135.92, 139.68, 143.67, 144.27, 148.65, 152.95, 155.02.

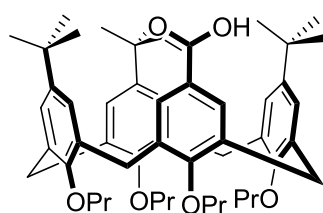
11,17,23-tri-*tert*-butyl-5-iodo-25,26,27,28-tetrapropoxycalix[4]arene [12]¹³

A combination of amino calixarene **11** (4.0 g, 5.08 mmol) and *para*-toluene sulfonic acid (3.0 g, 15.3 mmol, 3.1 eq) was taken up in acetonitrile (20 ml) in a 100 ml round-bottomed flask and stirred for 15 minutes at room temperature. Thereafter, the solution was cooled to 10 °C. Sodium nitrite (0.7 g,

10.16 mmol, 2 eq) and potassium iodide (2.1 g, 12.7 mmol, 2.5 eq) were dissolved in H₂O (approx. 4 ml). The salt solution was cautiously added to the reaction mixture over 5 minutes, with rapid stirring. The reaction mixture was stirred for an hour, slowly warming to room temperature. H₂O was subsequently added to the flask (50 ml). The mixture was extracted with dichloromethane (2 x 75 ml). The combined organics were washed successively with 10% sodium thiosulfate solution (10 ml) and saturated NaHCO₃ solution (100 ml). The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. The residue was purified by crystallization from dichloromethane (10 ml) and ethanol (90 ml) to give **12** as fine white crystals (3.5 g, 3.91 mmol, 76%). Characterisation data conformed to literature data.¹³

Mp 196 °C (EtOH/DCM); R_f = 0.75 (100% PET); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.88 (s, 9H, C(CH₃)₃), 0.94 (t, *J* = 7.5 Hz, 6H, CH₂CH₃), 1.04 - 1.13 (m, 6H, CH₂CH₃), 1.34 (s, 18H, C(CH₃)₃), 1.85 - 1.98 (m, 4H, CH₂CH₂CH₃), 1.99 - 2.13 (m, 4H, CH₂CH₂CH₃), 3.07 (d, *J* = 12.6 Hz, 2H, ArCH₂Ar), 3.15 (d, *J* = 12.9 Hz, 2H, ArCH₂Ar), 2.66 (t, *J* = 7.0 Hz, 2H, OCH₂CH₂), 3.72 (t, *J* = 7.0 Hz, 2H, OCH₂CH₂), 3.90 - 4.03 (m, 4H, OCH₂CH₂), 4.37 (d, *J* = 12.7 Hz, 2H, ArCH₂Ar), 4.44 (d, *J* = 12.7 Hz, 2H, ArCH₂Ar), 5.30 - 5.32 (m, 2H, ArH), 6.37 (s, 2H, ArH), 6.73 (s, 2H, ArH), 7.00 (d, *J* = 2.3 Hz, 2H, ArH), 7.11 (d, *J* = 2.3 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ ppm 9.88, 10.61, 10.78, 23.05, 23.33, 23.55, 30.70, 31.14, 31.44, 31.66, 33.66, 34.07, 76.54, 77.13, 77.31, 77.49, 85.70, 124.58, 125.00, 126.08, 132.09, 134.37, 135.85, 136.34, 136.14, 144.27, 144.79, 152.78, 154.70, 155.26.

11,17,23-tri-*tert*-butyl-5-carboxy-25,26,27,28-tetrapropoxycalix[4]arene [**13**]¹³

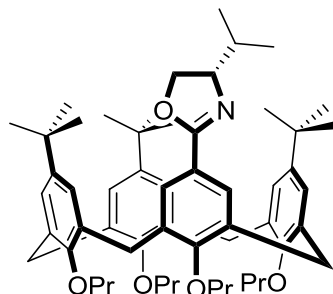


Iodo calixarene **12** (4.1 g, 4.6 mmol) was weighed out into an oven-dried Schlenk flask and placed under high vacuum with heating to 90 °C for 5 hours. The crystals were dissolved in dry THF (3 ml) and the solvent carefully removed under reduced pressure. The flask was once again heated to 90 °C under high vacuum for 1 hour. The flask was then cooled to 0 °C and *i*PrMg·LiCl₂ in THF (20 ml, 18.5 mmol, 4 eq) was added slowly under a positive pressure of argon. The flask was stirred for 90 minutes, while slowly warming to room temperature. The reaction mixture was poured onto freshly condensed powdered CO₂ (400 ml). After warming to room temperature, the residue was dissolved

in DCM (200 ml) and washed with 1M HCl (50 ml), H₂O (100 ml) and saturated NaHCO₃ solution (50 ml). The solvent was removed under reduced pressure and the solid residue purified by column chromatography (15% EtOAc in PET) to produce **13** as a white solid (2.21 g, 2.75 mmol, 60%). Characterisation data conformed to literature data.¹³

Mp 285 °C (EtOH/DCM); *R*_f = 0.21 (10% EtOAc in PET); ¹H NMR (300 MHz, CDCl₃) δ ppm, 0.69 (s, 9H, C(CH₃)₃), 0.94 (t, *J* = 7.5 Hz, 6H, CH₂CH₃), 1.06 - 1.14 (m, 6H, CH₂CH₃), 1.36 (s, 18H, C(CH₃)₃), 1.85 - 1.98 (m, 4H, CH₂CH₂CH₃), 2.00 - 2.11 (m, 4H, CH₂CH₂CH₃), 3.09 - 3.20 (m, 4H, ArCH₂Ar), 3.67 - 3.76 (m, 4H, OCH₂CH₂), 3.90 - 4.08 (m, 4H, OCH₂CH₂), 4.42 (d, *J* = 7.5 Hz, 2H, ArCH₂Ar), 4.46 (d, *J* = 7.5 Hz, 2H, ArCH₂Ar), 6.26 (s, 2H, ArH), 7.11 (br. s., 4H, ArH), 7.18 (s, 2H, ArH), 10.55 - 11.70 (br. s., COOH); ¹³C NMR (75 MHz, CDCl₃) 9.89, 10.64, 10.81, 23.08, 23.41, 23.57, 30.87, 31.14, 31.67, 33.23, 34.10, 76.50, 76.58, 77.32, 77.43, 123.03, 124.47, 125.35, 126.14, 129.96, 132.05, 133.96, 134.63, 135.85, 144.30, 144.89, 152.70, 154.70, 159.99, 171.33.

11,17,23-tri-*tert*-butyl-5-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-25,26,27,28-tetrapropoxycalix[4]arene [14]¹³

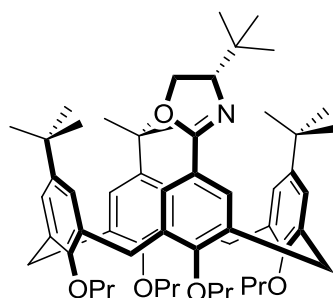


Carboxylic acid calixarene **13** (1.60 g, 1.92 mmol) and freshly distilled thionyl chloride (5 ml, 69 mmol, 36 eq) were placed in a 2-necked round-bottomed flask fitted with a reflux condenser and stirred for 10 minutes at room temperature before being brought to reflux for 2 hours. The excess thionyl chloride was removed under reduced pressure while maintaining inert conditions. The solid residue was dissolved in dry DCM, which was subsequently removed under reduced pressure to remove any remaining thionyl chloride. The acid chloride was once again dissolved in dry DCM, and added dropwise to a stirring solution of L-valinol (290 mg, 2.9 mmol, 1.5 eq), Et₃N (1.2 ml, 9 mmol, 4.7 eq) and dry DCM (10 ml) at 0 °C (under a positive pressure of argon). The solution was then warmed to room temperature and stirred overnight. The contents of the flask were added to DCM (50 ml) and washed with saturated NaHCO₃ solution (30 ml). The aqueous phase was extracted with DCM (3 x 100 ml). The combined organics were dried over MgSO₄ and the solvent removed under

reduced pressure. The solid residue was dried under high vacuum for 2 hours, before being dissolved in dry DCM (20 ml) and transferred to an oven-dried round-bottomed flask under argon. Thionyl chloride (2 ml, 28 mmol, 14 eq) was added to the flask under a positive pressure of argon and the solution stirred for 12 hours at room temperature. Water was carefully added to the flask until there was no more frothing. Following this, saturated NaHCO_3 (30 ml) and DCM (50 ml) were added. The layers were separated and the aqueous layer was extracted with DCM (3 x 100 ml). The combined organics were dried over MgSO_4 and the solvent removed under reduced pressure. Purification by column chromatography (gradient elution: 1% EtOAc in PET to 20% EtOAc in PET) yielded the oxazoline **14** as a white solid (1.60 g, 1.84 mmol, 93%). Characterisation data conformed to literature data.¹³

Mp 176-178 °C (EtOH); $R_f = 0.70$ (10% EtOAc in PET); $[\alpha]_D^{19} = -17.0^\circ$ (c 0.10, DCM); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.75 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.83 (d, $J = 6.7$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 0.91 - 1.00 (m, 9H, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$), 1.04 (t, $J = 6.7$ Hz, 3H, CH_2CH_3), 1.17 (t, $J = 6.7$ Hz, 3H, CH_2CH_3), 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.33 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.62 - 1.71 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.85 - 1.98 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.99 - 2.13 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.09 - 3.20 (m, 4H, ArCH_2Ar), 3.67 - 3.83 (m, 6H, OCH_2CH_2 , OCH_2CN , OCH_2CH_N), 4.18 - 4.23 (m, 1H, OCH_2CH_N), 4.43 - 4.57 (m, 4H, ArCH_2Ar), 6.30 (d, $J = 1.9$ Hz, 2H, ArH), 7.04 (d, $J = 1.9$ Hz, 1H, ArH), 7.07 - 7.09 (m, 3H, ArH), 7.12 (d, $J = 2.9$ Hz, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ 9.91, 9.92, 10.63, 10.77, 18.54, 19.39, 23.06, 23.12, 23.36, 23.54, 30.77, 30.87, 30.93, 31.08, 31.13, 31.64, 33.23, 33.34, 34.05, 70.09, 72.80, 76.51, 76.58, 77.00, 77.21, 121.57, 124.32, 124.79, 125.40, 125.45, 125.80, 125.86, 127.64, 128.00, 132.13, 123.31, 133.55, 133.66, 134.71, 134.83, 135.59, 135.69, 143.84, 144.63, 144.71, 152.82, 154.69, 157.95, 163.19.

11,17,23-tri-*tert*-butyl-5-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-25,26,27,28-tetrapropoxycalix[4]arene [15]¹⁴

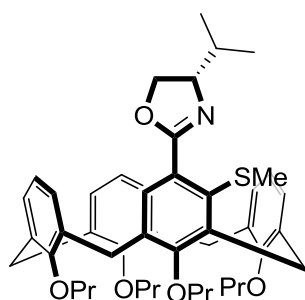


Calixarene **15** was synthesised using a procedure analogous to that used for the synthesis of **14**, from carboxylic acid **13** (552 mg, 0.687 mmol) and thionyl chloride (3 ml, 41 mmol, 60 eq), then L-

tert-leucinol (100 mg, 0.82 mmol, 1.2 eq) and Et₃N (0.34 ml, 2.5 mmol, 3.6 eq) in DCM (5 + 10 ml) and finally additional thionyl chloride (0.8 ml, 11.3 mmol, 16.4 eq) in DCM (10 ml). Purification was achieved via column chromatography (2% EtOAc in PET) to yield **15** as a pale yellow solid (571 mg, 0.64 mmol, 94%). Characterisation data conformed to literature data.¹⁴

Mp 208-210 °C (EtOH/DCM); R_f = 0.85 (10% EtOAc in PET); [α]_D²⁵ = −10.4° (c 2.2, DCM); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.77 (s, 9H, C(CH₃)₃), 0.85 (s, 9H, C(CH₃)₃), 0.95 (t, *J* = 7.4 Hz, 6H, CH₂CH₃), 1.03 - 1.12 (m, 6H, CH₂CH₃), 1.30 (s, 9H, C(CH₃)₃), 1.86 - 1.99 (m, 4H, CH₂CH₂CH₃), 1.99 - 2.14 (m, 4H, CH₂CH₂CH₃), 3.09 - 3.20 (m, 4H, ArCH₂Ar), 3.68 - 3.75 (m, 4H, OCH₂CH₃), 3.76 - 3.82 (m, 1H, NCHCH₂), 3.89 - 4.01 (m, 5H, OCH₂CH₂, OCH₂CH), 4.11 (dd, *J* = 9.9, 8.5 Hz, 1H, OCH₂CH), 4.40 - 4.46 (m, 4H, ArCH₂Ar), 6.34 (d, *J* = 2.5 Hz, 1H, ArH), 6.37 (d, *J* = 2.5 Hz, 1H, ArH), 7.02 - 7.07 (m, 3H, ArH), 7.07 - 7.11 (m, 2H, ArH), 7.13 (d, *J* = 2.0 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 9.97, 10.61, 10.72, 23.10, 23.15, 23.34, 23.52, 26.04, 30.74, 30.84, 30.98, 31.06, 31.09, 31.61, 33.39, 33.62, 34.04, 68.19, 76.08, 76.57, 76.69, 77.05, 77.19, 121.78, 124.28, 125.00, 125.39, 125.43, 125.69, 125.75, 127.67, 127.89, 132.25, 132.49, 133.366, 133.73, 135.54, 134.70, 135.39, 135.50, 143.95, 144.63, 144.66, 152.86, 154.56, 154.58, 157.92, 163.17.

(*cR*)-5-((*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-tetrapropoxycalix[4]arene [16-A]⁹

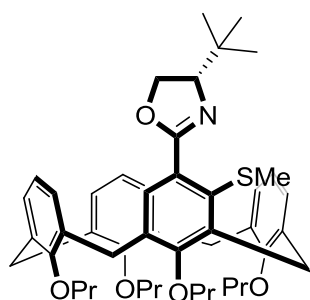


Typical ortholithiation reaction procedure: Pre-dried isopropyl oxazoline **6** (170 mg, 0.241 mmol) was placed in an oven-dried Schlenk flask, together with TMEDA (0.36 ml, 2.34 mmol, 10 eq) and dry pentane (5 ml). The flask was cooled to −78 °C and *c*-PentLi (1.5 ml, 1.20 mmol, 5 eq) was added dropwise. The flask was sealed and stirred for 5 hours at −78 °C. Thereafter, dimethyl disulfide (0.40 ml, 4.5 mmol, excess) was slowly added and the flask allowed to warm to room temperature overnight. H₂O (5 ml) and EtOAc (10 ml) were added to the flask, which was stirred for 5 minutes. Additional EtOAc (50 ml) and H₂O (50 ml) were added and the layers separated. The aqueous phase was extracted with a further portion of EtOAc (50 ml), the organic layers were combined and were

dried over MgSO_4 . The solvent was removed under reduced pressure to yield a light yellow semi-solid, **16-A**. Yield by ^1H NMR 93%. Selectivity by ^1H NMR 94% de. Further purification could be achieved by silica gel column chromatography (3% EtOAc in PET) (161 mg, 0.215 mmol, 89%) Characterisation data conformed to literature data.⁹

$R_f = 0.55$ (10% EtOAc in PET); $[\alpha]_D^{22} = -11.5^\circ$ (c 1.3, DCM); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.85 - 0.92 (m, 6H, CH_2CH_3), 1.04 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.06 - 1.14 (m, 9H, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$), 1.81 - 2.02 (m, 9H, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$), 2.41 (s, 3H, SCH_3), 3.15 (d, $J = 13.5$ Hz, 1H, ArCH_2Ar), 3.16 (d, $J = 13.5$ Hz, 1H, ArCH_2Ar), 3.17 (d, $J = 13.8$ Hz, 1H, ArCH_2Ar), 3.61 - 3.78 (m, 4H, OCH_2CH_2), 3.97 - 4.06 (m, 4H, OCH_2CH_2), 4.14 - 4.26 (m, 2H, ArCH_2Ar , OCH_2CHN), 4.28 - 4.36 (m, 2H, OCH_2CHN), 4.38 - 4.54 (m, 4H, ArCH_2Ar), 5.97 (dd, $J = 7.7$, 1.3 Hz, 1H, ArH), 6.05 (dd, $J = 7.6$, 1.3 Hz, ArH), 6.09 - 6.19 (m, 3H, ArH), 6.23 (d, $J = 7.7$ Hz, 1H, ArH), 6.92 (t, $J = 7.4$ Hz, 1H, ArH), 7.11 (d, $J = 7.4$ Hz, 2H, ArH), 7.35 (s, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 9.82, 10.79, 18.48, 18.95, 21.30, 22.97, 23.49, 27.34, 30.70, 30.96, 31.00, 32.86, 70.47, 72.82, 76.45, 76.68, 76.91, 77.21, 121.75, 122.20, 122.25, 127.04, 127.25, 127.52, 127.63, 128.81, 128.92, 129.96, 132.79, 133.05, 133.29, 133.47, 137.02, 137.17, 137.51, 142.25, 155.02, 155.08, 158.01, 160.22, 165.34.

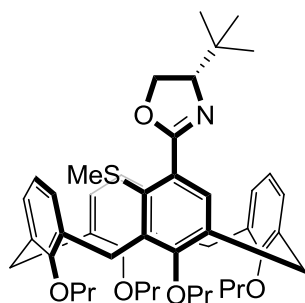
(*cR*)-5-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-tetrapropoxycalix[4]arene [17-A]¹⁴



Thioether oxazoline **17-A** was synthesised according to the general procedure described to synthesise **16-A** using oxazoline **7** (20 mg, 0.027 mmol), *s*-BuLi (0.15 ml, 0.14 mmol, 5 eq), TMEDA (0.04 ml, 0.28 mmol, 10 eq), pentane (0.5 ml) and dimethyl disulfide (0.1 ml, 1 mmol, excess). Yield by ^1H NMR 95%. Selectivity by ^1H NMR >99% de. Further purification could be achieved by silica gel column chromatography (3% EtOAc in PET) (19 mg, 0.025 mmol, 91%) Characterisation data conformed to literature data.¹⁴

$R_f = 0.51$ (10% EtOAc in PET); $[\alpha]_D^{25} = -3.5^\circ$ (c 1.0, DCM); ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 0.89 - 1.08 (m, 6H, CH_2CH_3), 1.06 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.10 - 1.25 (m, 6H, CH_2CH_3), 1.81 - 2.02 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.42 (s, 3H, SCH_3), 3.12 - 3.22 (m, 3H, ArCH_2Ar), 3.62 - 3.78 (m, 5H, ArCH_2Ar , OCH_2CH_2), 4.01 - 4.07 (m, 4H, OCH_2CH_2), 4.13 (dd, $J = 10.2, 8.2$ Hz, 1H, OCH_2CHN), 4.29 - 4.35 (m, 2H, OCH_2CHN), 4.39 - 4.50 (m, 4H, ArCH_2Ar), 5.97 (dd, $J = 7.5, 1.4$ Hz, 1H, ArH), 6.06 (dd, $J = 7.5, 1.4$ Hz, 1H, ArH), 6.10 - 6.19 (m, 3H, ArH), 6.24 (t, $J = 7.6$ Hz, 1H, ArH), 6.92 (t, $J = 7.6$ Hz, 1H, ArH), 7.11 (d, $J = 7.5$ Hz, 2H, ArH), 7.34 (s, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 9.81, 10.79, 21.34, 22.98, 23.50, 26.12, 27.28, 30.73, 30.90, 30.98, 31.01, 34.03, 69.00, 76.47, 76.67, 76.70, 76.93, 77.20, 121.76, 122.21, 122.27, 127.06, 127.27, 127.56, 127.65, 128.83, 128.94, 129.07, 129.95, 132.03, 132.78, 133.05, 133.29, 133.44, 136.13, 137.04, 137.19, 137.57, 142.34, 155.03, 155.09, 158.03, 160.23, 165.38.

(*cS*)-5-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-tetrapropoxycalix[4]arene [17-B]¹⁴

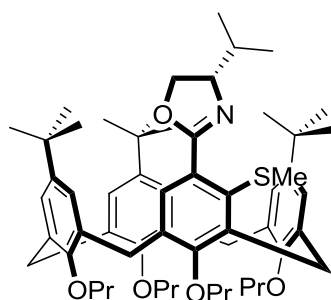


Thioether oxazoline **17-B** was synthesised according to the general procedure described to synthesise **16-A** using oxazoline **7** (20 mg, 0.027 mmol), *t*-BuLi (0.15 ml, 0.14 mmol, 5 eq), TMEDA (0.04 ml, 0.28 mmol, 10 eq), pentane (0.5 ml) and dimethyl disulfide (0.1 ml, 1 mmol, excess). Yield by ^1H NMR 75%. Selectivity by ^1H NMR 92% de. Further purification could be achieved by silica gel column chromatography (3% EtOAc in PET) (15 mg, 0.020 mmol, 70%) Characterisation data conformed to literature data.¹⁴

$R_f = 0.51$ (10% EtOAc in PET); $[\alpha]_D^{23} = -4.1^\circ$ (c 1.3, DCM); ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 0.89 - 1.09 (m, 6H, CH_2CH_3), 1.06 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.10 - 1.25 (m, 6H, CH_2CH_3), 1.81 - 2.02 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.42 (s, 3H, SCH_3), 3.12 - 3.22 (m, 3H, ArCH_2Ar), 3.62 - 3.78 (m, 5H, ArCH_2Ar , OCH_2CH_2), 4.00 - 4.07 (m, 4H, OCH_2CH_2), 4.13 (dd, $J = 10.2, 8.2$ Hz, 1H, OCH_2CHN), 4.29 - 4.36 (m, 2H, OCH_2CHN), 4.39 - 4.50 (m, 4H, ArCH_2Ar), 5.97 (dd, $J = 7.5, 1.4$ Hz, 1H, ArH), 6.06 (dd, $J = 7.5, 1.4$ Hz, 1H, ArH), 6.10 - 6.19 (m, 3H, ArH), 6.24 (t, $J = 7.6$ Hz, 1H, ArH), 6.92 (t, $J = 7.6$ Hz, 1H, ArH), 7.11 (d, $J = 7.5$ Hz, 2H, ArH), 7.31 (s, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 9.81, 10.79, 21.34, 22.98, 23.50, 26.12,

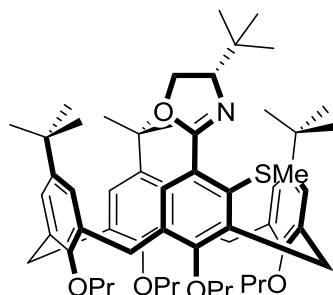
27.28, 30.73, 30.90, 30.98, 31.01, 34.03, 69.00, 76.47, 76.67, 76.70, 76.93, 77.20, 121.76, 122.21, 122.27, 127.06, 127.27, 127.56, 127.65, 128.83, 128.94, 129.07, 129.95, 132.03, 132.78, 133.05, 133.29, 133.44, 136.13, 137.04, 137.19, 137.57, 142.34, 155.03, 155.09, 158.03, 160.23, 165.38.

(*cR*)-11,17,23-tri-*tert*-butyl-5-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-calix[4]arene [18-A]¹³



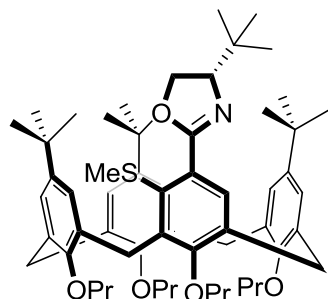
Thioether oxazoline **18-A** was synthesised according to the general procedure described to synthesise **16-A** using oxazoline **14** (180 mg, 0.207 mmol), *c*-PentLi (0.37 ml, 2.48, 12 eq), TMEDA (0.37 ml, 2.48 mmol, 12 eq), Et₂O (2 ml) and dimethyl disulfide (0.4 ml, 4.5 mmol, 20 eq). Yield by ¹H NMR 73%. Selectivity by ¹H NMR 93% de. Further purification could be achieved by silica gel column chromatography (3% EtOAc in PET) (135 mg, 0.147 mmol, 71%). Characterisation data conformed to literature data.¹³

Mp 80 °C (DCM); *R*_f = 0.43 (10% EtOAc in PET); [α]_D¹⁸ = -9.4° (*c* 0.012, DCM); ¹H NMR (400 MHz, CDCl₃) δ ppm, 0.93 - 1.08 (m, 36H, CH(CH₃)₂, CH₂CH₃, C(CH₃)₃), 1.81 - 2.09 (m, 12H, SCH₃, CH(CH₃)₂, CH₂CH₂CH₃), 3.15 - 3.25 (m, 2H, ArCH₂Ar), 3.68 - 3.95 (m, 8H, OCH₂CH₂, ArCH₂Ar, OCH₂CHN), 4.02 - 4.17 (m, 3H, ArCH₂Ar), 4.31 - 4.40 (m, 2H, ArCH₂Ar, OCH₂CHN), 4.40 - 4.47 (m, 3H, ArCH₂Ar), 6.67 (d, *J* = 2.2 Hz, 2H, ArH), 6.75 (d, *J* = 2.2 Hz, 2H, ArH), 6.81 - 6.88 (m, 2H, ArH), 7.19 (s, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ ppm 10.12, 10.27, 10.35, 10.46, 18.50, 19.11, 21.31, 22.88, 22.90, 23.32, 23.43, 28.68, 30.54, 31.17, 31.37, 31.43, 31.47, 31.50, 32.95, 33.77, 33.79, 33.82, 70.01, 72.94, 76.51, 76.63, 76.69, 76.81, 124.63, 124.68, 125.01, 125.14, 125.33, 125.82, 129.23, 130.16, 132.01, 132.02, 133.06, 133.08, 133.46, 134.12, 134.50, 135.82, 140.77, 143.75, 144.38, 144.41, 153.56, 153.65, 154.06, 158.79, 164.92.

(cR)-11,17,23-tri-*tert*-butyl-5-((S)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-calix[4]arene [19-A]¹⁴

Thioether **19-A** was synthesised according to the general procedure used to synthesise **16-A**, from oxazoline **15** (60 mg, 0.068 mmol), *s*-BuLi (0.3 ml, 0.34 mmol, 5 eq), TMEDA (0.1 ml, 0.68 mmol, 10 eq), Et₂O (1 ml) and dimethyl disulfide (0.1 ml, 10 mmol, excess). Further purification could be achieved by silica gel column chromatography (3% EtOAc in PET) (49 mg, 0.053 mmol, 78%). Characterisation data conformed to literature data.¹⁴

R_f = 0.40 (10% EtOAc in PET); $[\alpha]_D^{24} = -8.4^\circ$ (*c* 1.0, DCM); ¹H (400 MHz, CDCl₃) δ ppm 0.94 - 1.03 (m, 30H, C(CH₃)₃, CH₂CH₃), 1.04 (s, 9H, C(CH₃)₃), 1.13 (s, 9H, C(CH₃)₃), 1.87 - 2.10 (m, 11H, SCH₃, CH₂CH₂CH₃), 3.15 (d, *J* = 12.6 Hz, 2H, ArCH₂Ar), 3.16 (d, *J* = 12.6 Hz, 1H, ArCH₂Ar), 3.69 - 3.75 (m, 1H, OCH₂CH₂), 3.76 - 3.94 (m, 7H, OCH₂CH₂), 4.00 - 4.06 (m, 1H, OCH₂CHN), 4.10 - 4.18 (m, 2H, OCH₂CHN, ArCH₂Ar), 4.27 - 4.32 (m, 1H, OCH₂CHN), 4.34 (d, *J* = 12.9 Hz, 1H, OCH₂CHN), 4.39 - 4.42 (d, *J* = 12.6 Hz, 1H, ArCH₂Ar), 4.44 (d, *J* = 12.6 Hz, 2H, ArCH₂Ar), 6.67 (br. s., 2H, ArH), 6.75 (s, 1H, ArH), 6.77 (br. s., 1H, ArH), 6.84 (br. s., 1H, ArH), 6.86 (s, 1H, ArH), 7.16 (s, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ ppm 10.11, 10.27, 10.35, 10.46, 21.47, 22.90, 23.31, 23.44, 26.13, 28.63, 28.65, 29.70, 30.53, 31.18, 31.37, 31.42, 31.52, 33.76, 33.78, 33.83, 33.90, 68.49, 76.58, 76.66, 76.81, 77.20, 124.63, 124.69, 125.00, 125.15, 125.31, 125.79, 125.83, 129.75, 130.01, 131.99, 132.93, 133.08, 133.44, 134.12, 134.51, 135.95, 140.77, 143.77, 144.38, 144.44, 153.55, 153.65, 154.06, 158.70, 165.02.

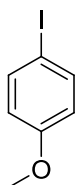
(cS)-11,17,23-tri-*tert*-butyl-5-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-calix[4]arene [19-B]¹⁴

Thioether oxazoline **19-B** was synthesised according to the general procedure described to synthesise **16-A** using oxazoline **15** (25 mg, 0.028 mmol), *t*-BuLi (0.15 ml, 0.14 mmol, 5 eq), TMEDA (0.04 ml, 0.28 mmol, 10 eq), pentane (0.5 ml) and dimethyl disulfide (0.1 ml, 1 mmol, excess). Yield by ¹H NMR 50%. Selectivity by ¹H NMR 75% de. Further purification could be achieved by silica gel column chromatography (3% EtOAc in PET) (18 mg, 0.020 mmol, 70%) Characterisation data conformed to literature data.¹⁴

$R_f = 0.40$ (10% EtOAc in PET); $[\alpha]_D^{26} = -7.1^\circ$ (c 1.0, DCM); ¹H (300 MHz, CDCl₃) δ ppm 0.94 - 1.03 (m, 30H, C(CH₃)₃, CH₂CH₃), 1.04 (s, 9H, C(CH₃)₃), 1.13 (s, 9H, C(CH₃)₃), 1.87 - 2.10 (m, 11H, SCH₃, CH₂CH₂CH₃), 3.15 (d, $J = 12.6$ Hz, 2H, ArCH₂Ar), 3.15 (d, $J = 12.6$ Hz, 1H, ArCH₂Ar), 3.69 - 3.75 (m, 1H, OCH₂CH₂), 3.76 - 3.96 (m, 7H, OCH₂CH₂), 4.00 - 4.06 (m, 1H, OCH₂CHN), 4.10 - 4.18 (m, 2H, OCH₂CHN, ArCH₂Ar), 4.27 - 4.32 (m, 1H, OCH₂CHN), 4.33 (d, $J = 12.9$ Hz, 1H, OCH₂CHN), 4.39 - 4.42 (d, $J = 12.6$ Hz, 1H, ArCH₂Ar), 4.44 (d, $J = 12.6$ Hz, 2H, ArCH₂Ar), 6.67 (br. s., 2H, ArH), 6.75 (s, 1H, ArH), 6.77 (br. s., 1H, ArH), 6.84 (br. s., 1H, ArH), 6.86 (s, 1H, ArH), 7.13 (s, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ ppm 10.11, 10.27, 10.35, 10.46, 21.47, 22.90, 23.31, 23.44, 26.13, 28.63, 28.65, 29.70, 30.53, 31.18, 31.37, 31.42, 31.52, 33.76, 33.78, 33.83, 33.90, 68.49, 76.58, 76.66, 76.81, 77.20, 124.63, 124.69, 125.00, 125.15, 125.31, 125.79, 125.83, 129.75, 130.01, 131.99, 132.93, 133.08, 133.44, 134.12, 134.51, 135.95, 140.77, 143.77, 144.38, 144.44, 153.55, 153.65, 154.06, 158.70, 165.02.

5.2.2. Model Compounds

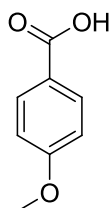
1-iodo-4-methoxybenzene [20]



To a round-bottomed flask were added successfully 4-iodophenol (6.1 g, 27.7 mmol), sodium carbonate (7.6 g, 71.8 mmol), acetonitrile (90 ml) and dimethyl sulfate (7.3 ml, 80.2 mmol). The mixture was stirred under argon and heated to reflux. After 24 hours, the reaction was diluted with water (50 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic layers were dried over MgSO_4 and the solvent removed by rotary evaporation. The residue was purified by silica gel chromatography (20% EtOAc in PET) yielding a **20** as a white solid (5.739 g, 24.5 mmol, 89%). Characterisation data conformed to literature data.

Mp 49-51 °C; R_f = 0.65 (30% EtOAc in PET); ^1H NMR (300 MHz, CDCl_3) δ ppm 3.79 (s, 3H, OCH_3), 6.68 (d, J = 9.0 Hz, 2H, ArH), 7.55 (d, J = 9.0 Hz, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 54.88 (OCH_3), 82.24 (C_{AR}), 115.91 (2 X C_{AR}), 137.75 (2 X C_{AR}), 159.01 (C_{AR}).

4-methoxybenzoic acid [21]

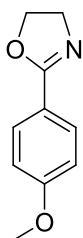


4-iodoanisole **20** (1.49 g, 6.37 mmol) was placed in an oven-dried round-bottomed flask and dried under vacuum overnight. THF (50 ml) was added to the flask and the contents stirred under argon. Sodium hydride (35 mg, 60% dispersion in mineral oil) was added and the flask cooled to -78 °C. *n*-BuLi (8.3 ml, 8.28 mmol) was slowly added. The pink solution was stirred for 15 minutes before being poured onto freshly condensed powdered CO_2 . Once the solution had reached room temperature, the contents were treated with 1M HCl (50 ml) and extracted with EtOAc (3 x 50 ml). The solvent was removed under reduced pressure and the product crystallised from toluene to yield beige

needle-like crystals of **21** (629 mg, 4.49 mmol, 71%). Characterisation data conformed to literature data.

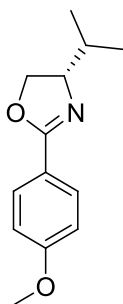
Mp 182-184 °C; R_f = 0.18 (30% EtOAc in PET); ^1H NMR (300 MHz, CDCl_3) δ ppm 3.89 (s, 3H, OCH_3), 6.95 (d, J = 8.9 Hz, 2H, ArH), 8.07 (d, J = 8.9 Hz, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 55.06 (OCH_3), 113.32 (2 X C_{AR}), 121.21 (C_{AR}), 131.92 (2 X C_{AR}), 163.61 (C_{AR}), 171.17 (COOH).

2-(4-methoxyphenyl)-4,5-dihydrooxazole [22]



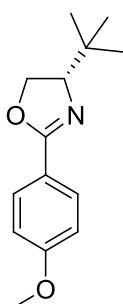
4-methoxybenzoic acid **21** (100 mg, 0.71 mmol) was placed in an oven-dried 100 ml round-bottomed flask and suspended in dry DCM (50 ml). Oxalyl chloride (0.30 ml, 3.55 mmol) was added and the mixture stirred under argon overnight. While maintaining inert conditions, the solvent and excess $(\text{COCl})_2$ were removed. Ethanolamine (0.10 ml, 101.6 mg, 1.66 mmol) was added to an oven-dried 50 ml 2-necked round-bottomed flask and placed under argon flow. 20 ml of dry DCM was injected through a septum, followed by Et_3N (1.5 ml) and the mixture stirred at 0 °C. The acid chloride was suspended in dry DCM (20 ml) and added to the amino alcohol mixture using a syringe pump at a flow rate of 35 ml per hour. Once all the acid chloride had been added, the mixture was allowed to warm to room temperature and stirred for two hours. The solution was transferred to a separate dry round-bottomed flask and the solvent removed by rotary evaporation. To this flask was added mesyl chloride (0.16 ml, 2.13 mmol), Et_3N (0.4 ml, 2.84 mmol) and dry DCM (20 ml). The mixture was stirred under argon and monitored by TLC. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography (10% EtOAc in PET), yielding an off-white solid, **22** (109 mg, 0.61 mmol, 87%). Characterisation data conformed to literature data.

Mp 60-62 °C; R_f = 0.22 (40% EtOAc in PET); ^1H NMR (300 MHz, CDCl_3) δ ppm 3.85 (s, 3H, OCH_3), 4.01 (t, J = 9.9 Hz, 2H, $\text{NCH}_2\text{CH}_2\text{O}$), 4.38 (t, J = 9.9 Hz, 2H, $\text{NCH}_2\text{CH}_2\text{O}$), 6.90 (d, J = 8.9 Hz, 2H, ArH), 7.88 (d, J = 8.9 Hz, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 54.83 ($\text{NCH}_2\text{CH}_2\text{O}$), 55.31 (OCH_3), 67.48 ($\text{NCH}_2\text{CH}_2\text{O}$), 113.65 (C_{AR}), 120.26 (C_{AR}), 129.83 (C_{AR}), 161.98 (C_{AR}), 164.41 ($\text{OC}(\text{Ar})=\text{N}$).

(S)-4-isopropyl-2-(4-methoxyphenyl)-4,5-dihydrooxazole [23]

23 was prepared in a procedure analogous to that used for **22** from **21** (100 mg, 0.71 mmol) and L-valinol (89mg, 0.86 mmol). Purification was achieved by silica gel chromatography (10% EtOAc in PET), yielding a beige solid (112 mg, 0.51 mmol, 72%). Characterisation data conformed to literature data.

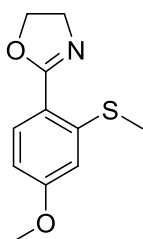
Mp 54-57 °C; R_f = 0.56 (40% EtOAc in PET); $[\alpha]_D^{24} = -66.5^\circ$ (c 1.03, DCM); ^1H NMR (300 MHz, CDCl_3) δ ppm 0.98 (d, J = 6.8 Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.08 (d, J = 6.8 Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.86 (d, J = 6.8 Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 3.84 (s, 3H, OCH_3), 4.06 - 4.09 (m, 1H, NCH), 4.34 - 4.36 (m, 1H, OCH_2CH), 4.37 - 4.39 (m, 1H, OCH_2CH), 6.74 (dd, J = 8.6, 2.5 Hz, 2H, ArH), 7.87 (dd, J = 8.6, 2.5 Hz, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 19.46 ($\text{CH}(\text{CH}_3)_2$), 32.61 ($\text{CH}(\text{CH}_3)_2$), 55.85 (OCH_3), 71.89 (OCH_2), 75.65 (NCH), 111.23 (C_{AR}), 122.02 (C_{AR}), 130.37 (C_{AR}), 161.45 (C_{AR}), 165.83 ($\text{OC}(\text{Ar})=\text{N}$) .

(S)-4-tert-butyl-2-(4-methoxyphenyl)-4,5-dihydrooxazole [24]

24 was prepared in a procedure analogous to that used for **22** from **21** (500 mg, 3.56 mmol) and L-tert-leucinol (428 mg, 3.66 mmol). Purification was achieved by silica gel chromatography (10% EtOAc in PET), yielding **24** as an off-white solid (598 mg, 2.56 mmol, 72%). Characterisation data conformed to literature data.

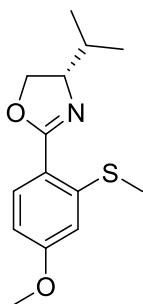
Mp 53-55 °C; R_f = 0.66 (40% EtOAc in PET); $[\alpha]_D^{24} = -18.8^\circ$ (c 0.25, DCM); ^1H NMR (300 MHz, CDCl_3) δ ppm 0.89 (s, 9H, $\text{C}(\text{CH}_3)_3$), 3.85 (s, 3H, OCH_3), 4.02 (dd, J = 10.0, 7.5 Hz, 1H, NCH), 4.21 (dd, J = 8.7, 7.5 Hz, 1H, OCH), 4.32 (dd, J = 10.0, 8.5 Hz, 1H, OCH), 6.89 (d, J = 8.9 Hz, 2H, ArH), 7.89 (d, J = 8.9 Hz, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 25.85 ($\text{C}(\text{CH}_3)_3$), 34.02 ($\text{C}(\text{CH}_3)_3$), 55.31 (OCH_3), 68.57 (OCH_2), 76.10 (NCH), 113.55 (C_{AR}), 120.50 (C_{AR}), 129.90 (C_{AR}), 161.87 (C_{AR}), 162.95 ($\text{OC}(\text{Ar})=\text{N}$).

2-(4-methoxy-2-(methylthio)phenyl)-4,5-dihydroxazole [25]



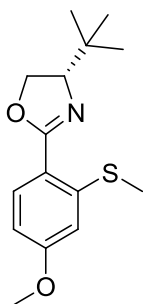
Oxazoline **22** (41 mg, 0.176 mmol) was dried overnight under high vacuum. An oven-dried 10 ml Schlenk flask equipped with magnetic stirrer was cooled under vacuum and filled with argon. The oxazoline was weighed out into the flask and dry THF (3.5 ml) added. *i*-PrLi (0.48 ml, 0.264 mmol) was carefully added to the stirring solution, which was subsequently stirred for 1.5 hours at -78°C . After this time, the solution was quenched with dimethyl disulfide (0.10 ml, 1.13 mmol) and stirred at -78°C for a further 30 minutes. The solution was thereafter allowed to warm to room temperature. After 2 hours, distilled water (2 ml) was added. After 20 minutes of additional stirring, the solution was poured into water (30 ml) and extracted with EtOAc (2 x 40 ml). The combined organics were dried over MgSO_4 and the solvent removed under reduced pressure. To remove any remaining dimethyl disulfide, the residue was dissolved in methanol and the solvent once again removed. Yield by ^1H NMR 73%. Further purification was achieved by flash chromatography (20% EtOAc in PhMe) to yield **25** as a yellow oil (28 mg, 0.125 mmol, 71%). Characterisation data conformed to literature data.

R_f = 0.58 (40% EtOAc in PhMe); ^1H NMR (300 MHz, CDCl_3) δ ppm 2.46 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 4.13-4.20 (m, 2H, $\text{NCH}_2\text{CH}_2\text{O}$), 4.32-4.39 (m, 2H, $\text{NCH}_2\text{CH}_2\text{O}$), 6.66 (dd, J = 8.6, 2.4 Hz, 1H, ArH), 6.77 (d, J = 2.4 Hz, 1H, ArH), 7.83 (d, J = 8.6 Hz, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 14.69 (SCH_3), 55.59 (OCH_3), 67.53 (OCH_2), 68.19 (NCH), 106.55 (C_{AR}), 110.41 (C_{AR}), 127.24 (C_{AR}), 128.59 (C_{AR}), 130.39 (C_{AR}), 142.94 (C_{AR}), 165.10 ($\text{OC}(\text{Ar})=\text{N}$).

(S)-4-isopropyl-2-(4-methoxy-2-(methylthio)phenyl)-4,5-dihydrooxazole [26]

26 was prepared in a procedure analogous to that used for **25** from oxazoline **23** (41 mg, 0.187 mmol). Yield by ^1H NMR 83%. Further purification was achieved by flash chromatography (20% EtOAc in PhMe) to yield **26** as a yellow-orange oil (40 mg, 0.150 mmol, 80%). Characterisation data conformed to literature data.

$R_f = 0.47$ (30% EtOAc in PhMe); $[\alpha]_D^{24} = -70.2^\circ$ (c 0.16, DCM); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.95 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.06 (d, $J = 6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.84 (d, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 2.44 (s, 3H, SCH_3), 3.86 (s, 3H, OCH_3), 4.06 - 4.09 (m, 1H, NCH), 4.15 - 4.21 (m, 1H, OCH_2CH), 4.31 - 4.35 (m, 1H, OCH_2CH), 6.65 (dd, $J = 8.6, 2.5$ Hz, 1H, ArH), 6.76 (d, $J = 2.5$ Hz, 1H, ArH), 7.77 (d, $J = 8.6$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 15.93 (SCH_3), 19.68 ($\text{CH}(\text{CH}_3)_2$), 33.50 ($\text{CH}(\text{CH}_3)_2$), 55.69 (OCH_3), 67.53 (OCH_2), 69.24 (NCH), 107.59 (C_{AR}), 110.62 (C_{AR}), 124.25 (C_{AR}), 129.99 (C_{AR}), 132.59 (C_{AR}), 158.94 (C_{AR}), 162.14 ($\text{OC}(\text{Ar})=\text{N}$).

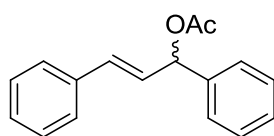
(S)-4-tert-butyl-2-(4-methoxy-2-(methylthio)phenyl)-4,5-dihydrooxazole [27]

27 was prepared in a procedure analogous to that used for **25** from oxazoline **24** (41 mg, 0.176 mmol). Yield by ^1H NMR 89%. Further purification was achieved by flash chromatography (20% EtOAc in PhMe) to yield **27** as a yellow oil (43 mg, 0.153 mmol, 87%). Characterisation data conformed to literature data.

$R_f = 0.39$ (20% EtOAc in PhMe); $[\alpha]_D^{24} = -122.4^\circ$ (c 0.40, DCM); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.99 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.43 (s, 3H, SCH_3), 3.86 (s, 3H, OCH_3), 3.93 - 4.34 (m, 3H, OCH_2CHN), 6.64 (dd, $J = 8.6$, 2.5 Hz, 1H, ArH), 6.76 (d, $J = 2.5$ Hz, 1H, ArH), 7.75 (d, $J = 8.6$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl_3) δ ppm 15.61 (SCH_3), 25.54 ($\text{C}(\text{CH}_3)_3$), 33.76 ($\text{C}(\text{CH}_3)_3$), 55.00 (OCH_3), 67.35 (OCH_2), 68.27 (NCH), 107.53 (C_{AR}), 110.35 (C_{AR}), 113.24 (C_{AR}), 129.59 (C_{AR}), 131.37 (C_{AR}), 142.95 (C_{AR}), 161.06 ($\text{OC}(\text{Ar})=\text{N}$).

5.2.3. Asymmetric Catalysis

Rac-(E)-1,3-diphenylprop-2-enyl acetate [28]¹⁵



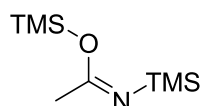
Magnesium (2.697 g, 111 mmol) and dry ether (80 ml) were added to a 250 ml two-necked round-bottomed flask. The solution was stirred under argon for 10 minutes. Bromobenzene (11.8 ml, 111 mmol) in ether (20 ml) was added drop wise to the solution. An iodine crystal was added to help initiate the reaction. The solution was brought to reflux for 30 min, following which the flask was removed from the heat source and left to stir at room temperature until the solution cooled. Cinnamaldehyde (9.5 ml, 75.5 mmol) in ether (15 ml) was then added drop-wise over 15 minutes. The solution was stirred for one hour at room temperature. The mixture was quenched with 2M HCl and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with brine (2 x 20 ml), dried over MgSO_4 and the solvent removed by rotary evaporation to yield a yellow-orange low melting solid.

The crude alcohol was dissolved in pyridine (20 ml), transferred to a clean 50 ml two-necked round-bottomed flask and stirred under argon. To this solution was added acetic anhydride (8 ml, 84.6 mmol) and DMAP (0.4150 g, 3.40 mmol). The solution was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and the residue diluted with 100 ml water. The solution was extracted with ethyl acetate (3 x 50 ml), washed with brine (2 x 50 ml) and dried over MgSO_4 . After removal of the solvent under reduced pressure, the desired acetate was purified by vacuum distillation to yield a yellow oil, **28** (13.7 g, 54.3 mmol, 72%). Characterisation data conformed to literature data.

Bp 165-170 °C (1 mmHg); $R_f = 0.45$ (10% EtOAc in PET); ^1H NMR (300 MHz, CDCl_3) δ ppm 2.18 (s, 3H, CH_3), 6.34 (dd, $J = 15.6$, 6.9 Hz, 1H, Ph-CH=CH), 6.46 (d, $J = 6$ Hz, 1H, Ph-CH(OAc)), 6.64 (d, $J = 15.6$

Hz, 1H, Ph-CH=CH), 7.26-7.46 (m, 10H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 21.31 (COCH_3), 76.11 (Ph-CH(OAc)), 126.66 (CH=CH-Ph), 127.01 (CH=CH-Ph), 127.47 (2 x C_{AR}), 128.02 (C_{AR}), 128.13 (C_{AR}), 128.45 (2 x C_{AR}), 128.59 (2 x C_{AR}), 132.55 (2 x C_{AR}), 136.14 (C_{AR}), 139.21 (C_{AR}), 169.97 (COCH_3).

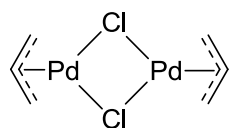
***N,O*-bis(trimethylsilyl)acetamide [29]**



Acetamide (4.0 g, 67.7 mmol) was added to an oven-dried 100 ml 2-necked round-bottomed flask under a positive pressure of argon. Dry diethyl ether (80 ml) was added to the flask and the solution stirred vigorously. Et_3N (20 ml, 149 mmol) was added and the solution stirred for 10 minutes at 0 °C. TMSCl (18 ml, 149 mmol) was then injected slowly over 10 minutes. The solution was stirred for 1 hour at 0 °C before allowing it to warm to room temperature. The supernatant was transferred by cannula to an oven-dried 100 ml round-bottomed flask. The residue was washed thrice with dry diethyl ether, each time transferring the supernatant. The solvent was removed from the filtrate while maintaining inert conditions, after which the desired compound **29** was distilled under reduced pressure (8.251 g, 40.6 mmol, 60%). Characterisation data conformed to literature data.

Bp 50 °C (20 mmHg); ^1H NMR (300 MHz, CDCl_3) δ ppm 0.07(s, 9H, N-Si(CH_3) $_3$), 0.24 (s, 9H, O-Si(CH_3) $_3$), 1.94 (s, 3H, C- CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 0.82 (O-Si(CH_3) $_3$), 1.92 (N-Si(CH_3) $_3$), 25.18 (CH_3 -C), 175.87 (O-C=N).

Allyl palladium(II) chloride dimer [30]¹⁶



PdCl_2 (500 mg, 2.8 mmol), NaCl (330 mg, 5.6 mmol) and water (20 ml) were added to a 50 ml two-necked flask. After 15 minutes of stirring under nitrogen, methanol was added (30 ml). Allyl chloride (0.70 ml, 8.6 mmol) was then slowly injected through a septum. The mixture was allowed to stir for 24 hours at room temperature. After this time, the yellow solution was poured into H_2O (100 ml) and extracted with CHCl_3 (2 x 50 ml). The combined organics are washed twice with water and dried

over MgSO_4 . The solvent was removed under reduced pressure to yield the corresponding dimer **30** as a bright yellow solid, which was then dried under high vacuum to constant weight (497 mg, 1.4 mmol, 97%).

General procedure for palladium-catalysed allylic substitutions

$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$ **30** (4 mg, 0.01 mmol, 2.5 mol %) was added to an oven-dried Schlenk flask under a positive pressure of argon. A solution of the appropriate ligand (0.04 mmol, 10 mol%) in dry DCM (1 ml) was added and the mixture was stirred for 30 minutes at room temperature. The solution was subsequently treated with a solution of (*E*)-1,3-diphenyl-prop-2-enyl acetate **28** (100 mg, 0.4 mmol) in dry DCM (1 ml), followed by dimethyl malonate (0.14 ml, 1.4 mmol), *N,O*-bis(trimethylsilyl)acetamide **29** (0.30 ml, 1.2 mmol) and lithium acetate (2 mg, 0.02 mmol). The reaction mixture was stirred at room temperature until complete consumption of starting material was observed by TLC. The solution was diluted with DCM (20 ml) and poured into ice-cold saturated aqueous ammonium chloride (50 ml). The layers were separated and the aqueous phase extracted with DCM (3 x 30 ml). The combined organics were dried over MgSO_4 before the solvent was removed by rotary evaporation. The residue was purified by flash chromatography (10% EtOAc in PET) to yield the product (*E*)-dimethyl 2-(1,3-diphenylallyl)malonate **31** as a colourless oil. Characterisation data conformed to literature data.

R_f = 0.30 (10% EtOAc in PET); ^1H NMR (300 MHz, CDCl_3) δ ppm 3.40 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 3.94 (d, J = 10.8 Hz, 1H, $\text{CH}(\text{CO}_2\text{CH}_3)_2$), 4.24 (dd, J = 10.8, 8.5 Hz, 1H, $\text{PhCHCH}(\text{CO}_2\text{CH}_3)_2$), 6.29 (dd, J = 15.9, 8.5 Hz, 1H, $\text{HC}=\text{CHPh}$), 6.46 (d, J = 15.9 Hz, 1H, $\text{HC}=\text{CHPh}$), 7.07-7.44 (m, 10H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 41.09 ($\text{PhCHCH}(\text{CO}_2\text{Me})_2$), 52.51 (OCH_3), 57.62 ($\text{CH}(\text{CO}_2\text{Me})_2$), 125.79-131.79 (C_{Ar} , $\text{C}=\text{C}$), 166.89 (CO_2Me).

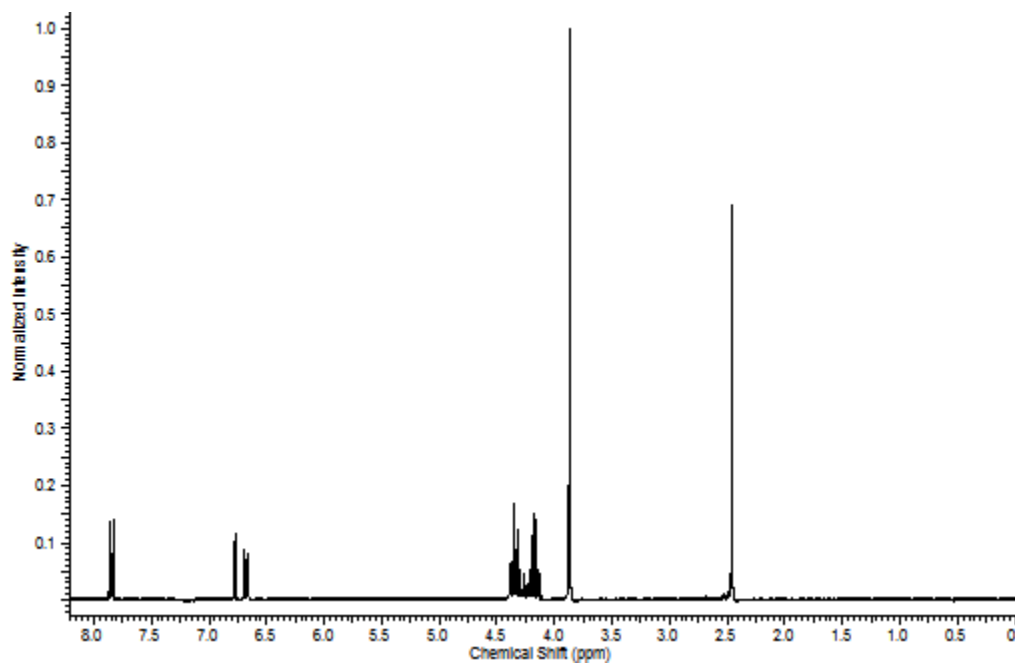
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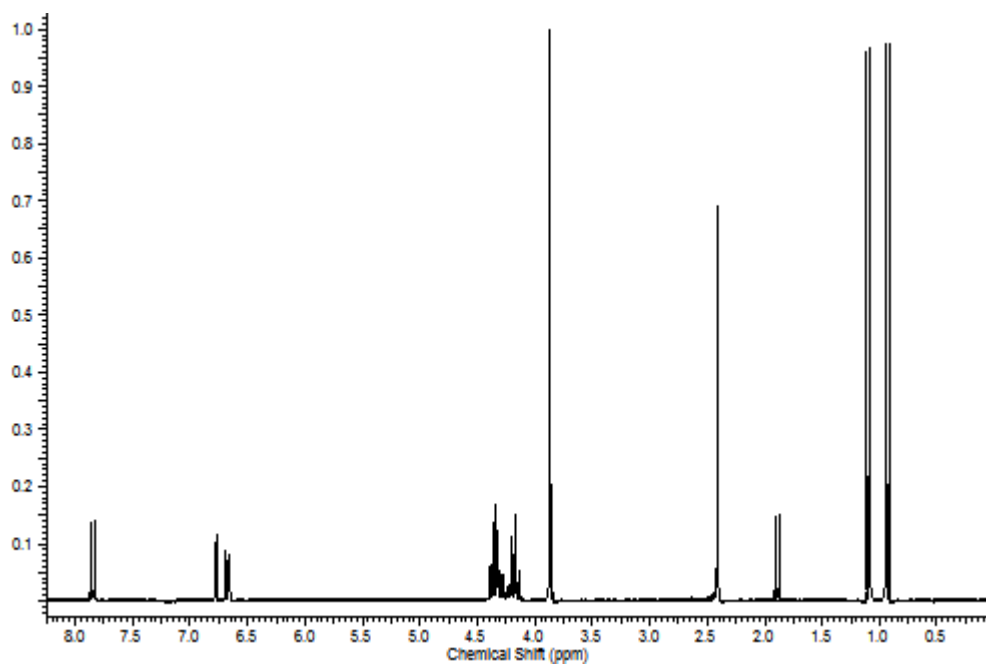
Appendix I

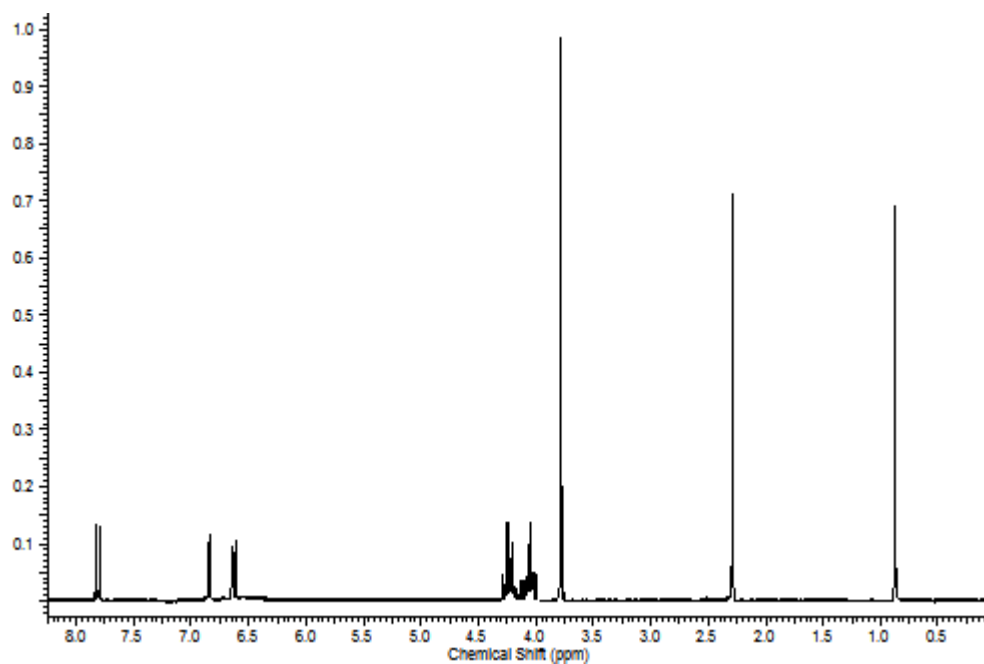
^1H NMR spectra of ligands

2-(4-methoxy-2-(methylthio)phenyl)-4,5-dihydroxazole [25]

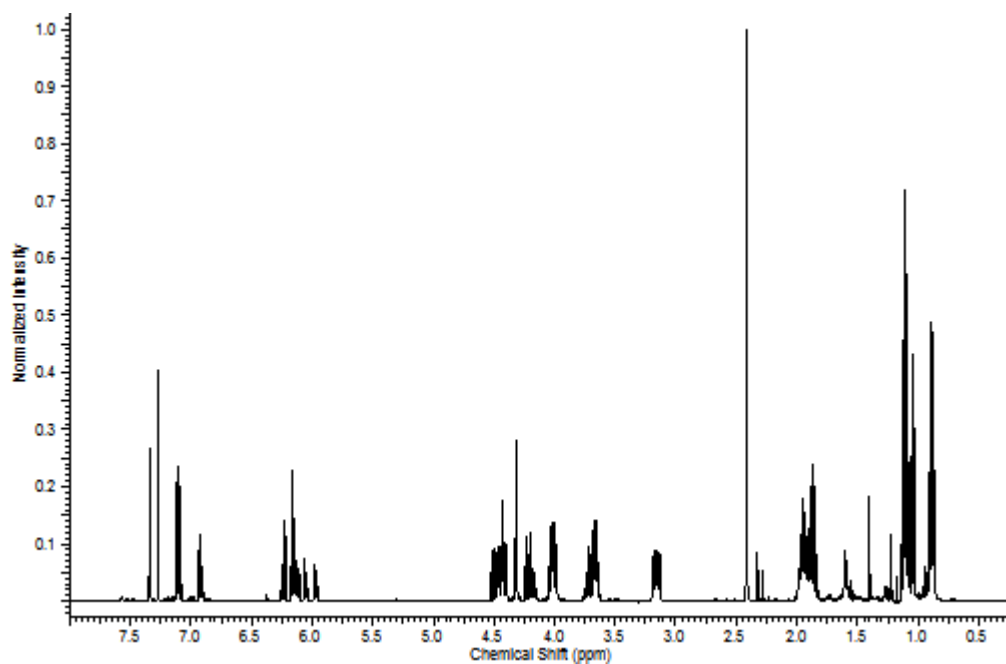


(S)-4-isopropyl-2-(4-methoxy-2(methylthio)phenyl)-4,5-dihydroxazole [26]

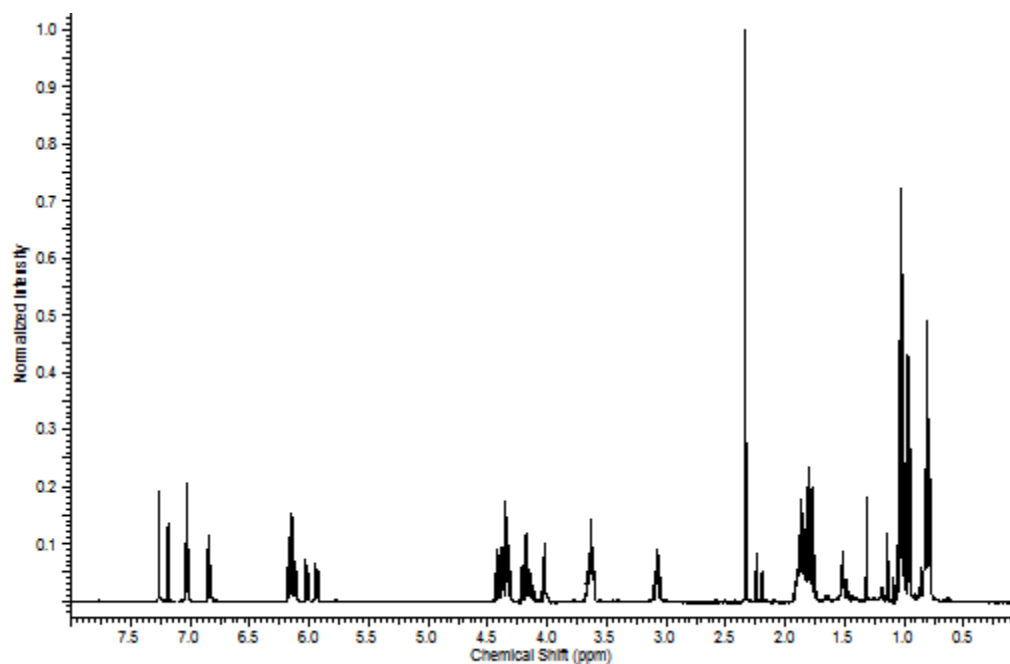


(S)-4-tert-butyl-2-(4-methoxy-2-(methylthio)phenyl)-4,5-dihydrooxazole [27]

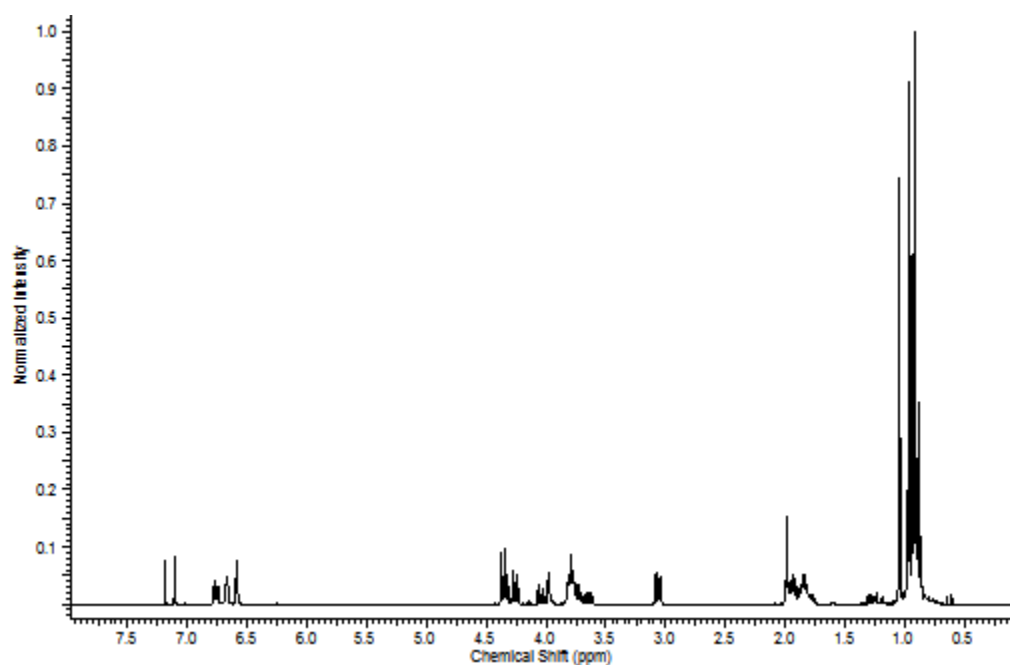
Calixarene ligands are presented as a mixture of **A** and **B** diastereomers.

5-((S)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-tetrapropoxycalix[4]arene [16]

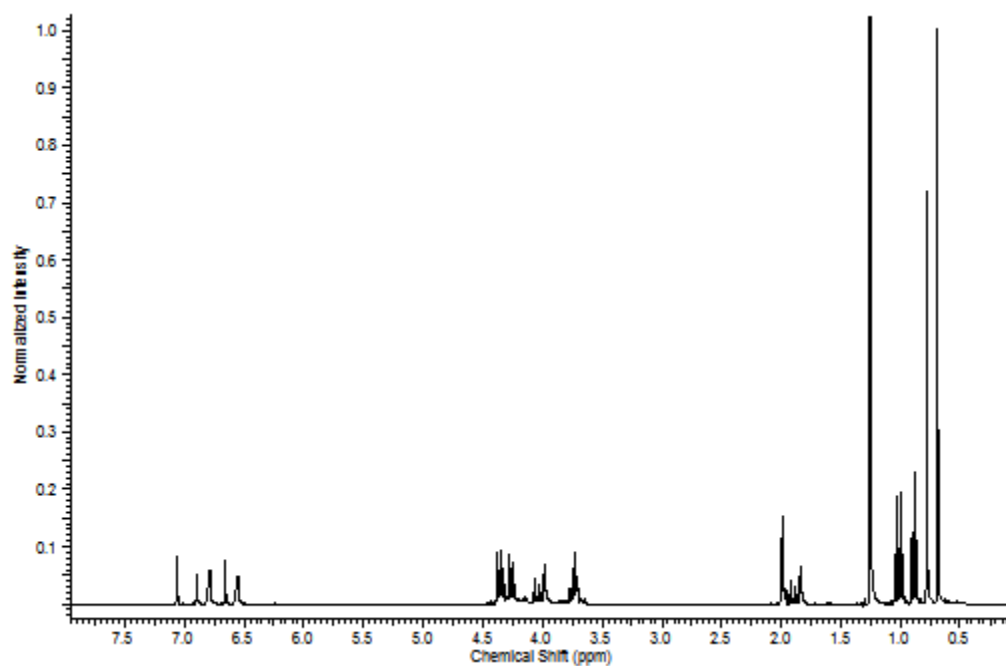
5-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-tetrapropoxycalix[4]arene [17]



11,17,23-tri-*tert*-butyl-5-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-calix[4]arene [18]



11,17,23-tri-*tert*-butyl-5-((*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl)-4-methylthio-25,26,27,28-calix[4]arene [19]



Appendix II

Chiral HPLC Results

Data

Table A1: HPLC Conditions

Column	Chiralpak IC (250 x 4.6 mm, 5 μ m)
Flow rate	3 mL/min
Temperature	40 °C
Detection	UV (254 nm)
Solvent	Hexane: Isopropanol 95:5
Rt ₁ (min)	5.83 (<i>R</i>)
Rt ₂ (min)	6.56 (<i>S</i>)
α	1.6

Table A2: HPLC Results

Ligand	t ₁ (rel %)	t ₂ (rel %)	ee (%)
M1	51.5	48.5	3
M2	28.5	71.5	43
M3	10.5	89.5	79
L1-A	33.5	66.5	33
L1-B	26	74	48
L2-A	12	88	76
L2-B	5	95	90

Chromatograms

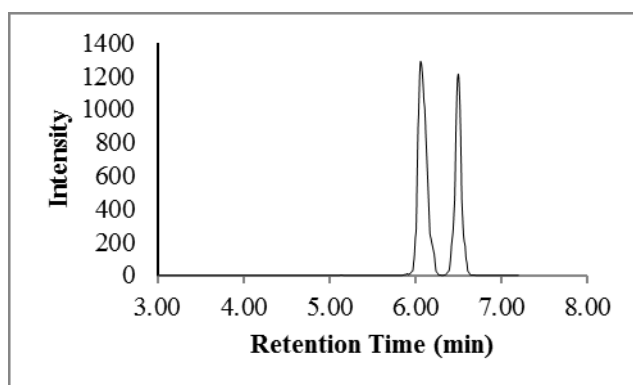


Figure A1: Ligand M1

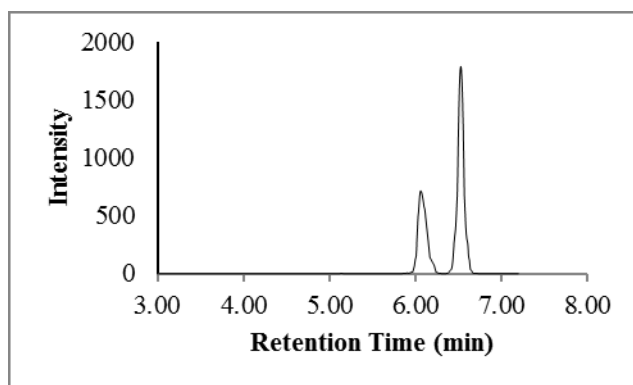


Figure A2: Ligand M2

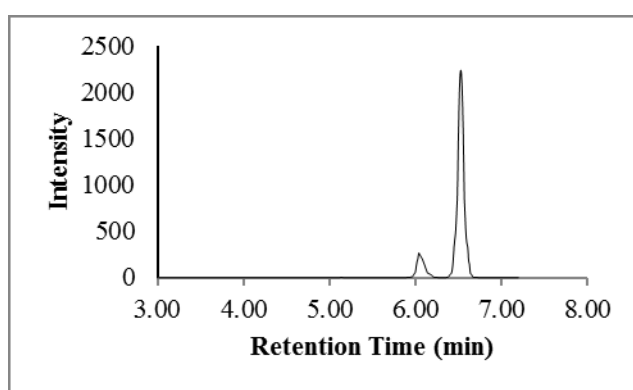


Figure A3: Ligand M3

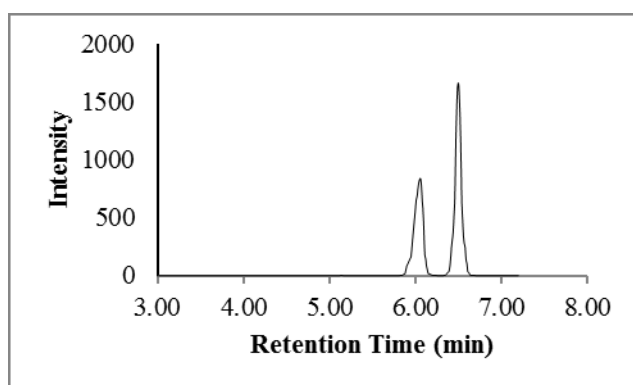


Figure A4: Ligand L1-A

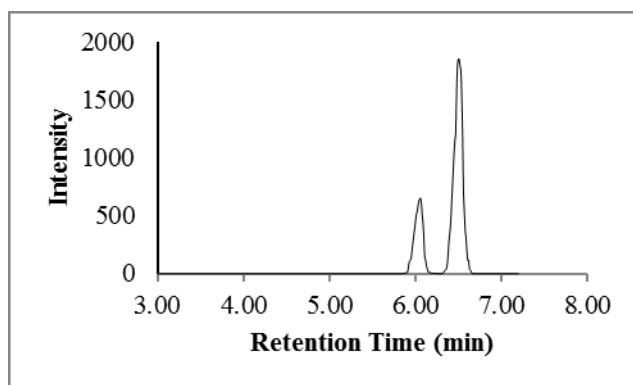


Figure A5: Ligand L1-B

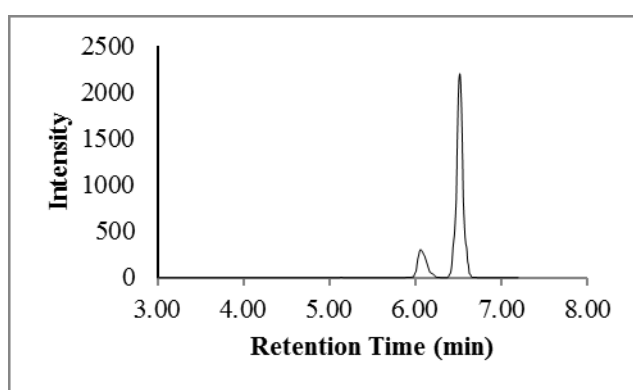


Figure A6: Ligand L2-A

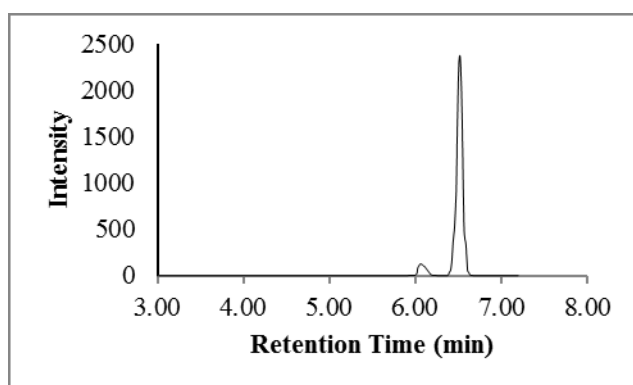


Figure A7: Ligand L2-B

Appendix III

Classification on Inherent Chirality

A convenient nomenclature for the description of inherent chirality has been proposed by Schiaffino and co-workers.¹ The methylene bridges of the calix[4]arene are assigned a priority, following standard IUPAC conventions. Standing at an observation point inside the curved system at the point of lowest priority, an ideal observer will see the three highest priority bridges in either a cyclic clockwise (*cR*) or anticlockwise (*cS*) pattern, where the *c* designates curvature.

Consequently, for the calix[4]arenes described in this thesis, the (*cR*) and (*cS*) diastereomers were identified as seen in figure A8.

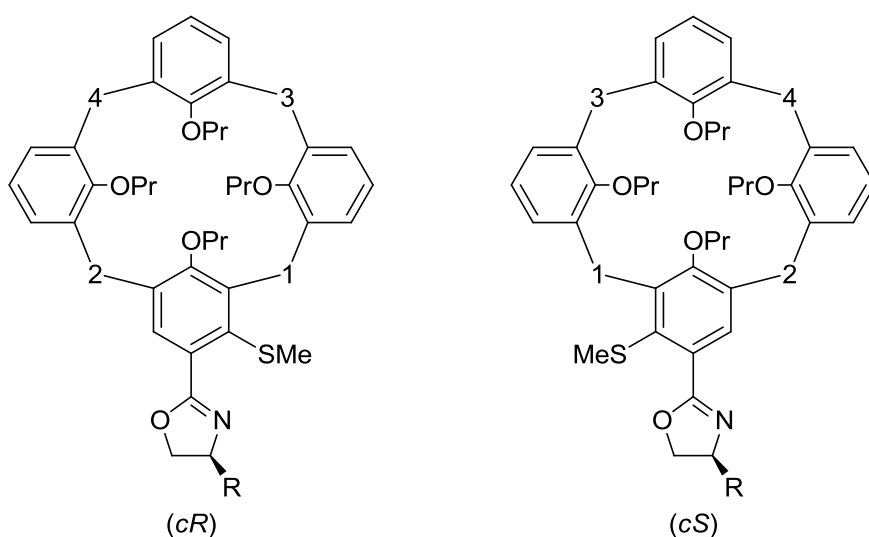


Figure A8: Classification of inherently chiral calixarenes

A. References

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